VOLUME 57 • JANUARY 1957 • NUMBER 1

OPHTHALMOLOGY

Changes in Aqueous Flow and Blood-Aqueous Barrier After Hydrochloric Acid Burns to the Eye
James H. Allen, John W. Manning Jr., Marion A. Guidry, and Joyce B. Kelly

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S. I. Askovitz

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Chordomas of Ocular Interest
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Pediatric Anesthesia
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II. Vitreous Humor, Normal Values
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Novobiocin, A New Antibiotic
Theodore W. Sery, Satya Dev Paul, and Irving H. Leopold

Neuromyelitis Optica with Increased Intracranial Pressure
Robert J. Keefe, and Dwight H. Trowbridge

Lips, Lacrimal Apparatus, and Conjunctiva
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Distance (plastic) lenses are being used with a strong aspheric magnifier in the lower portion of the lens. Such lens forms have been used in the past but the glass lens has the double disadvantage of additional weight and a serious reduction in field of any appreciably strong magnification due to the use of spherical surfaces. It should be noted that binocular vision cannot be successfully obtained in magnifications above 5X without the use of prisms. Therefore, the aspheric magnifications from 6X to 12X are for monocular use only.

A major fitting problem in all telescopic spectacles is their excessive weight. With the use of plastic lenses and lightweight plastic frames this problem will normally be obviated.

The majority of these lenses are new products and not all are as yet commercially available. However, the prototypes have been tested in various clinics and are in process of production. Mass-production methods of molding should keep their final price well within reach of the limited resources of elderly people who most often require these aids. It seems that no longer will you (and we) be forced to tell the majority of our patients with subnormal vision—"I'm sorry, but I can't help you".

"if it's a lens problem, let's look at it together"

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New Cover Design

With this issue, the A. M. A. ARCHIVES OF OPHTHALMOLOGY presents a new cover design and a slight modification of page format.

Two elements contribute to an attractive cover—simplicity and cleanliness. We believe that we have obtained the two primary objectives necessary in a cover design of this nature: namely, that it is attractive and that it conveys the subjective feeling of the unit which it represents, as well as legibility, which is important in this case because of the contents listing involved. This cover is fluid enough to attractively accommodate varying lengths of contents listing. By the use of a simple line or block treatment, and by placing the contents upon a white background, we gain the maximum contrast possible, therefore, greater legibility.

The use of the seal has several functions: Being a circle in design, it relieves to an extent the over-all use of lines, squares, and rectangles; it stands as a symbol for the many years of dedicated service by an organization of the American Medical Association's stature in the advancement of knowledge in specialized fields, thus adding immeasurably to the effectiveness of the design.

The change in page format is confined to the title, subtitle, and authors' names. The change from a Coronet Bold type face to Bodoni Bold will eliminate the difficulty encountered when reading a formula or an abbreviation in script capitals. The use of Antique Italic for subtitles and Spartan Bold for the authors creates a desirable distinction between these parts. The arrangement realizes a saving in space.

This new cover is a development of an idea. It is not the result of a sudden thought. First, a suggestion was presented which was nothing more than a different arrangement of familiar elements. Then followed the collection of reactions, suggestions, and additional experimentation in search for the inspiration. All of the separate bits of information gathered were thoroughly digested, and the relationship between elements was established. The result is the crystallization of the idea. In following this procedure, our readers and editors have contributed immeasurably to the end product. Their cooperation means a new design of lasting quality.

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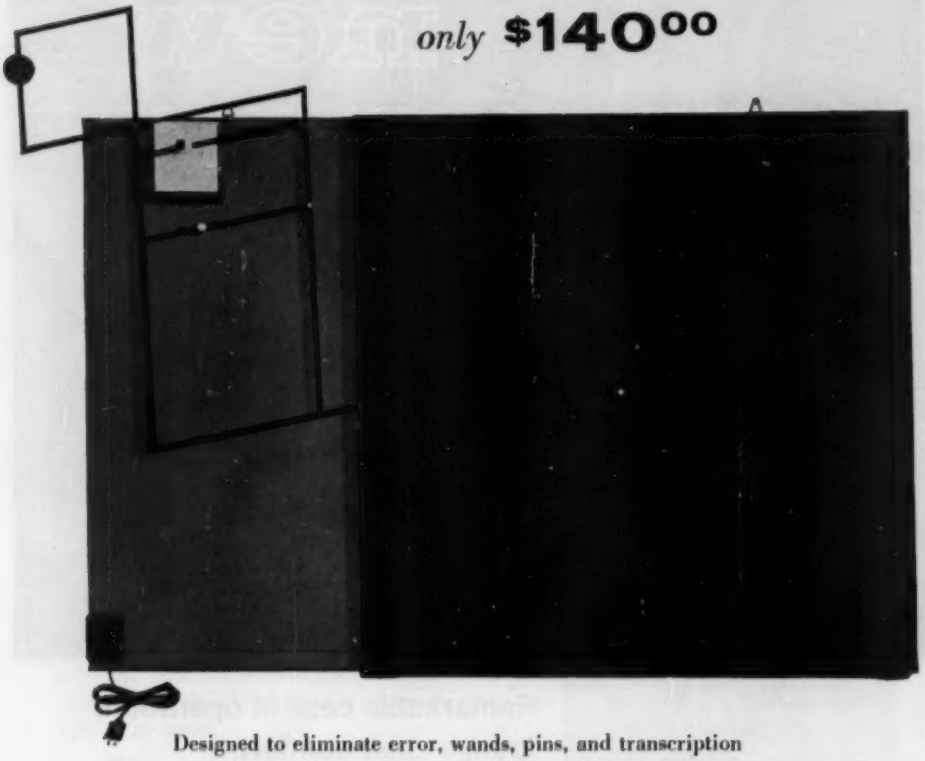

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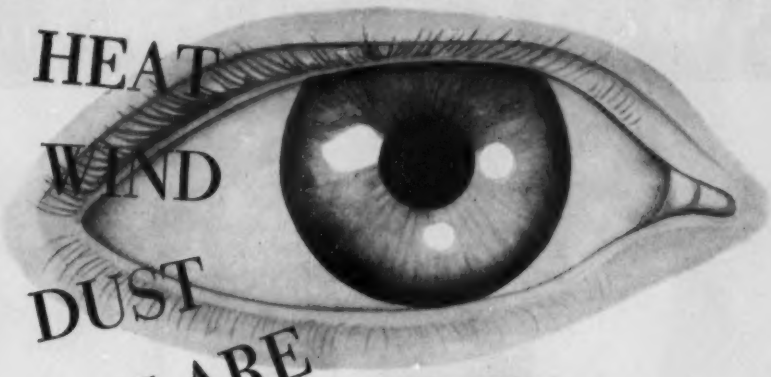

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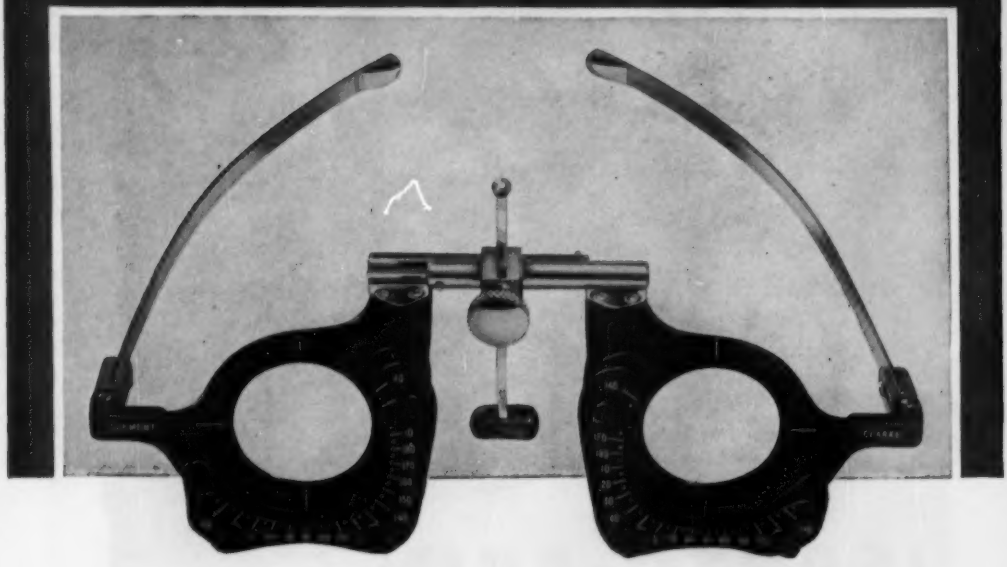

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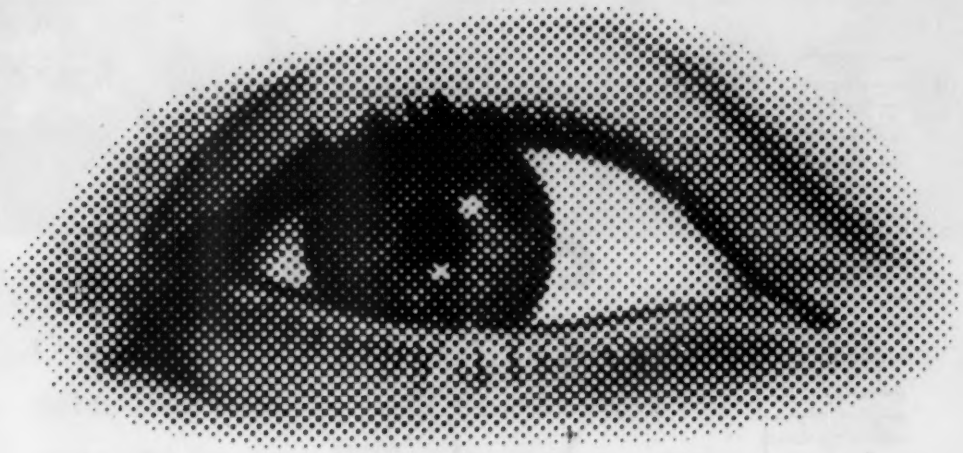

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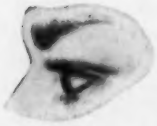

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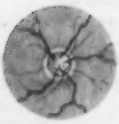

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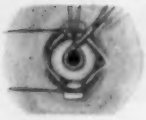

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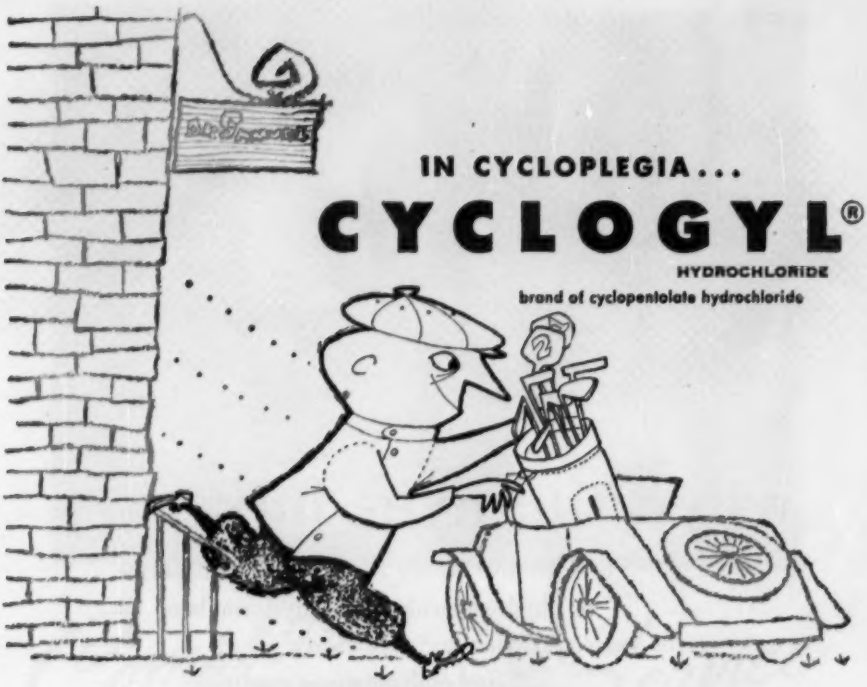

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1. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.

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Changes in Aqueous Flow and Blood-Aqueous Barrier After Hydrochloric Acid Burns to the Eye

JAMES H. ALLEN, M.D.; JOHN W. MANNING Jr., M.S.; MARION A. GUIDRY, Ph.D., and JOYCE B. KELLY, B.S., New Orleans

Introduction

In a previous communication from this laboratory [1] it was demonstrated that the ascorbic acid and lactate concentrations in the anterior aqueous humor of rabbits decrease after onset of hydrochloric acid injury to the cornea. The concentration of these materials remains lower than normal for three to four days. It was demonstrated that there was no increase in the rate of utilization of these substances by the anatomic components of the anterior segment of the injured eye. It was therefore concluded that the data were indirect evidence that an increase in permeability of the iris vessels occurred as a result of the acid injury.

It is the purpose of the present work to show by more direct means that an increase in permeability of the iris vessels as well as an increase in the rate of flow of the aqueous humor occurs in the rabbit eye after hydrochloric acid injury to the cornea.

Methods

p-Aminohippuric Acid Determination.—*p*-Aminohippuric acid was determined by the method of Smith and co-workers.[2] This method was modified only slightly so that the quantity of reagents used for developing color in the aqueous humor sample obtained a final dilution of 2 ml. The quantity of reagents used for plasma color development gave a final volume of 7 ml.

Standard Burning Technique.—A standard hydrochloric acid injury was applied to the cornea by a procedure previously reported.[1] The injury consisted of dropping 1 N hydrochloric acid on the exposed cornea at the rate of 1 drop (about 0.06 cc.) every 10 seconds from a standardized pipette for 1 minute. The eye was then immediately washed for 15 seconds with purified water.

Animal Care.—Albino rabbits of the New Zealand white breed weighing between 1.7 and 2.9 kg. were used in these experiments. The animals were housed in galvanized cages of the suspended type. They had free access to water and a diet of Gibbons Rabbit Pellets supplemented with approximately ¼ lb. of raw cabbage per day.

Experimental Procedure.—The disappearance rate and the steady state ratio (R) of test material were determined in separate animals. Both values could be obtained from the same animal by altering the procedure as described in Section C.

A. Disappearance Rate of Test Material (*p*-Aminohippuric Acid) from the Anterior Aqueous Humor: Unanesthetized rabbits

Received for publication June 11, 1956.

From the Department of Ophthalmology, Tulane University School of Medicine.

This study was supported by funds provided under contract AF-41(657)-2 with the U. S. A. F. School of Aviation Medicine, Randolph Field, Texas.

were selected at appropriate time intervals after acid injury to the cornea. They were given intravenously 500 mg. of *p*-aminohippuric acid per kilogram body weight through the marginal ear vein. Following the injection, 5 ml. blood samples were taken hourly for three hours by heart puncture. Simultaneously with the second- and third-hour blood samples, the aqueous humor was sampled. By puncturing the cornea with a 25-gauge needle, the contents of the anterior chamber of the aqueous humor were evacuated into a 0.25 ml. syringe. The volume of aqueous humor obtained by such a procedure ranged between 0.10 and 0.20 ml.

B. Determination of the Steady State Concentration Ratio, Aqueous/Plasma: Unanesthetized rabbits were restrained on a rabbit board. A 21-gauge needle was inserted and clamped in the intraperitoneal cavity. An infusion of test material (*p*-aminohippuric acid) was begun. A 1 mg. per 100 cc. solution of *p*-aminohippuric acid was continuously infused for three hours at the rate of 10 ml. per hour. In order initially to elevate the plasma level an injection of 0.28 mg. of *p*-aminohippuric acid per kilogram of body weight was given through the marginal ear vein. Blood samples (4 ml.) were taken every half hour by heart puncture. Two and one-half hours and three hours after the infusion had begun an aqueous humor sample was obtained as outlined in the above paragraph.

C. Simultaneous Determination of Steady State Ratio and Disappearance Rate: By modifying a procedure reported by Barany and Wirth,[3] which uniquely combines the above two methods, the steady state ratio and rate of flow in the same animal were determined at various time intervals after acid injury to the cornea. An unanesthetized rabbit was restrained on a rabbit board. Under local anesthesia (ethyl chloride) the femoral artery and vein were isolated in opposite legs. Into the femoral vein an appropriately sized cannula was inserted and 1 mg. per 100 cc. solution of *p*-aminohippuric acid was infused at the rate of 10 mg. per hour. An indwelling needle was inserted into the femoral artery of the opposite leg, from which blood samples were taken. The infusion was continuous for two hours, at which time the aqueous humor of one eye was removed and the infusion was stopped. One hour after the infusion was stopped the second aqueous sample was taken from the opposite eye. Blood samples were taken every 30 minutes for the first 2 hours during the infusion. In the last hour of the experiment blood samples were taken every 15 minutes.

Mathematical Considerations.—The mathematical analysis of the experimentally obtained data was that employed by Barany and Kinsey.[3,4] This considered, first, an adjustment for the steady state distribution ratio to correct for variation in plasma concentration and, second, an adjustment for the disappearance rate to correct for the concentration of material remaining in the plasma. The Fisher *t*-test of significance was used in calculating the probability of difference in the means.

Results

The distribution ratio, aqueous/plasma, of test material under steady-state conditions was determined in 3 controls and in 20 experimental rabbits. The control group showed a mean distribution ratio of 0.26, with a standard error of ± 0.006.

The distribution ratios, aqueous/plasma, of animals from the experimental group were measured 24 hours, 48 hours, 72 hours, and 96 hours after acid injury to the cornea. The *R*-values for each time period are given in Table 1. The mean distribution ratios (*R*-values) ranged from 0.30 to 0.48 for this group. The 48-hour group had the highest mean *R*-value. This value was statistically different from the control value.

The disappearance rates of the test material, *p*-aminohippuric acid, from the aqueous humor were measured in 12 control rabbits and in 36 experimental rabbits. The control group showed a mean disappearance

TABLE 1.—*The Mean Distribution Ratio* (R), *Aqueous/Plasma, of Control and Acid-Injured Eyes*

Time*	R	S.E.	P†
Control	0.26	±0.006	
24 hr	0.33	±0.056	0.5-0.4
48 hr	0.48	±0.009	0.02-0.01
72 hr	0.30	±0.033	0.4-0.3
96 hr	0.39	±0.058	0.2-0.1

* The number of hours after acid injury to the cornea that the determination was made.
† *P* values are the statistical difference from the control as obtained from the Fisher *t*-test.

rate (k_{out}) of 0.0144, with a standard error of ±0.0010. The results are presented in Table 2. The k_{out} values obtained for the 24-hour and 48-hour groups were significantly different from the control values.

The method of calculating the rate of flow from disappearance rate was that reported by Barany and Kinsey.[5] They have shown that the rate of change of concentration of test material in the aqueous is related to the difference between the concentrations of this material in plasma and aqueous humor by the following differential equation:

$$\frac{dC_{aq}}{dt} = k_{in}C_{pl} - k_{out}C_{aq} \quad (1)$$

where

k_{in} = rate of entrance into aqueous
k_{out} = rate of exit from aqueous
C_{pl} = concentration in the plasma
C_{aq} = concentration in the aqueous
t = time in minutes.

Under steady-state conditions the rate of change of C_{aq} equals zero, and

$$\frac{C_{aq}}{C_{pl}}_{\text{steady state}} = R = \frac{k_{in}}{k_{out}} \quad (2)$$

where

R = steady-state distribution ratio.

When the rate of entrance occurs by secretion, then

$$k_{in} = k_{secretion}$$

and

$$k_{out} = k_{flow} \quad (3)$$

where

k_{flow} = rate of loss by flow.

If diffusion is the process by which a substance enters the aqueous, then

$$k_{in} = k_{diff.}$$

and

$$k_{out} = k_{diff.} + k_{flow} \quad (4)$$

where

$k_{diff.}$ = rate of entrance and exit by diffusion. Thus, by substituting equation (2) in (4) and solving for k_{flow}

$$k_{flow} = k_{out}(1 - R) \quad (5)$$

Thus, for each k_{out} value calculated, two k_{flow} values can be obtained. When a substance is assumed to enter the aqueous chambers by secretion and to leave by virtue of the through and through circulation of the aqueous, then equation (3) holds. This is the upper limit of k_{flow}. If a substance enters by diffusion and leaves the aqueous by diffusion and flow, then equation (4) holds. Thus the lower limit of k_{flow} is calculated by equation (5).

TABLE 2.—*The Mean Rate of Disappearance* (k_{out}) *and the Rate of Flow* (k_{flow}) *of Control and of Acid-Injured Eyes at Various Time Intervals*

Time	k_{out}	S.E.	P*	k_{flow}†	S.E.	P*
Control	0.0144	±0.0010		0.0100	±0.0006	
24 hr	0.0261	±0.0003	0.001	0.0175	±0.0006	0.02-0.01
48 hr	0.0326	±0.0014	0.001	0.0169	±0.0007	0.001
72 hr	0.0179	±0.0023	0.2-0.1	0.0125	±0.0016	0.1-0.05
96 hr	0.0151	±0.0025	0.6-0.5	0.0092	±0.0016	0.3-0.2

* *P* values are the statistical difference from the normal as obtained from the Fisher *t*-test.
† $k_{flow} = k_{out}(1 - R)$.

The rates of flow as calculated by equation (5) for the 24- and 48-hour groups are significantly different from the control values so calculated. Table 2 shows the upper and lower limits for each group and their probability of difference from the control. Figure 1 represents the upper and lower limits of flow of the aqueous for each time interval after acid injury to the cornea. Examination of the graph shows that the rate of flow was increased after injury until the fourth day, at which time it fell to within a normal range.

Graphically, the relation between the steady-state distribution ratio (R) and the rate of disappearance (k_{out}) is shown in

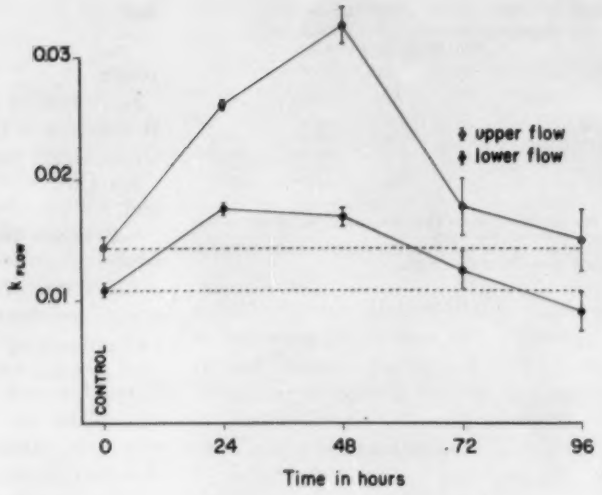

Fig. 1.—The upper and lower limits of flow as k_{flow}, at various time intervals following acid injury to the cornea.

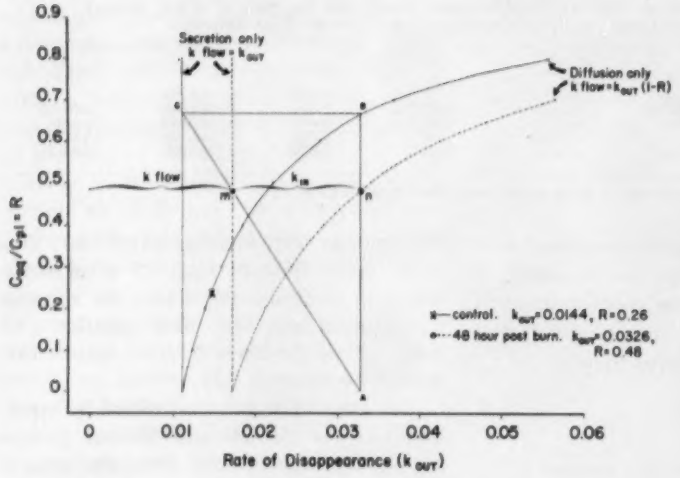

Fig. 2.—The graphic relationship of R and k_{out} of test material in normal and acid-injured eye.

Figure 2. The straight line curve parallel to the vertical axis represents the upper limits of flow when $k_{out}=k_{flow}$. The curvilinear line represents the lower limits of flow when $k_{flow}=k_{out}\ (1-R)$. The value obtained for the control group falls on the curve represented by equation (5).

The broken lines of Figure 2 are the curves obtained from the acid-injured eye 48 hours after injury. It is seen from this example that the rate of flow of the aqueous is increased. The rate of loss by diffusion is also increased above normal. These curves are displaced to the right of the normal curves.

From the construction of such a graph as that shown in Figure 2 the constants for entrance and loss of a given material from the aqueous humor may be derived. If a point falls in the field to the right of the normal curves, as in the case of the 48-hour group, its mode of entrance is by diffusion only. If, on the other hand, a point falls

between the two normal curves, then its mode of entrance is by secretion and diffusion.

The proportions of diffusion and secretion that determine the mode of entrance of a given material into the aqueous humor are derived by constructing a right triangle, *ABC*. A line is drawn through the observed point (*N*) perpendicular to the horizontal axis and intersects the curve $k_{flow}=k_{out}(1-R)$ at *B*. A perpendicular line is drawn from this intersect (*B*) to the curve $k_{flow}=k_{out}$ at Point *C*. The third side of the triangle is formed by the intersection of curve $k_{flow}=k_{out}$ (*C*) and the point on the horizontal axis to which the perpendicular though the observed point (*N*) has been drawn (*A*). If a fourth line be drawn from the observed point (*N*) perpendicular to the vertical axis, where this line intersects the third side of the triangle, this is the desired point (*M*). The distance from this point (*M*) to the vertical axis is k_{flow}, and the $k_{diff.}$ is the distance from the observed point (*N*) to Point *M*.

The values of the constants obtained graphically by this method are given in Table 3.

TABLE 3.—*The Constants of Entrance and Exit of Test Material from the Aqueous Humor of Control and Acid-Injured Eyes, Obtained Graphically*

Time	k_{out}	k_{flow}	k_{in}
Normal	0.0144	0.0110	0.0034
24 hr.	0.0261	0.0178	0.0083
48 hr.	0.0326	0.0170	0.0156
72 hr.	0.0179	0.0125	0.0054
96 hr.	0.0151	0.0092	0.0059

Comment and Conclusion

The mode of entrance of *p*-aminohippuric acid into the aqueous is by diffusion, as demonstrated in Figure 2. Under the experimental conditions employed, the rate of flow of the aqueous humor was increased after hydrochloric acid injury to the cornea. This increased rate of flow was sustained for three days following injury and returned to within normal range by the fourth day.

There was also an increase in the permeability of the blood-aqueous barrier, as demonstrated by an increase in the steady-state ratio (*R*). The increase in permeability was further shown by the increase in $k_{diff.}$ This increase in permeability was statistically significant for the first two days after injury and returned to within normal range by the fourth day.

In other studies from this laboratory [1] it was shown that the lactate concentration in the aqueous humor of acid-injured eyes decreased for the first three days following injury and returned to normal by the fourth day. The ascorbic acid content of the aqueous of burned eyes also showed a similar decrease in concentration compared with control levels. The concentration of ascorbic acid in the posterior chamber of acid-injured eyes did not differ from normal values. From the data presented, and those previously obtained in this laboratory, it is concluded that the permeability of the blood-aqueous barrier in the anterior chamber increases and that the rate of flow of aqueous increases after acid injury to the cornea.

It is also suggested that the secretory processes of the ciliary body are not altered. The decrease in ascorbic acid concentration in the anterior chamber aqueous humor after acid injury is due primarily to an increase in permeability of the blood-aqueous barrier.

Summary

The distribution ratio aqueous humor/plasma of *p*-aminohippuric acid under steady state conditions in acid-burned rabbit eyes was measured.

The disappearance rate of the same test material from the aqueous humor of acid-burned rabbit eyes was also determined.

The results show that there is an increase in the rate of flow of aqueous humor as well as an increase in permeability of the blood-aqueous barrier in these acid-

injured eyes which persists for four days after onset of injury under the experimental conditions employed.

Dr. Walter S. Wilde criticized the data.

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A Note on the Construction of the Schiötz Tonometer

Mathematical Analysis of the Hammer Contact Surface

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In a review article on tonometry several years ago,[1] a number of modifications in the construction of the conventional Schiøtz tonometer[2] were described. In particular, the shape of the hammer on the lever arm had been altered from the usual downward curve to an upward one in the form of an epicycloid. Statements were made concerning the superiority of this arrangement, but no supporting proofs or references were given.

An attempt to verify the mechanical principles led to an independent study of the most desirable shape for the contacting surface of the hammer. It will be shown that the theoretically ideal shape is that of the involute of a circle, rather than any epicycloid. Furthermore, the concave downward form with this curve provides practically the same advantages as the concave upward one. Nothing beyond the standard concepts of polar coordinates and the calculus will be required.

The essential premise upon which the subsequent development is based is that the contact between the hammer-and-pointer assembly and the upper end of the plunger be kept on a horizontal plane.[1] This is fairly evident, for whenever the hammer rests obliquely against the upper end of the plunger (Fig. 1), the weight of the hammer causes a lateral thrust of the plunger against its shaft, increasing frictional resistance and interfering with the smooth vertical motion of the plunger. Let us, therefore, inquire into the geometrical properties of the hammer such that a horizontal plane of contact will be insured at all times. It is obvious that only the under-surface of the hammer is concerned in this, and, furthermore, only that limited portion of the curve which may actually come into contact with the upper end of the plunger throughout the maximum excursion of the latter (Fig. 2).

Let AB represent the vertical line along which the central axis of the plunger is free to slide, and let O designate the fulcrum point about which the hammer-and-pointer assembly rotates. Draw OC perpendicular to AB, and let OCD represent the under-surface of the hammer. As the plunger tip slides up and down, it is clear that the point of contact on the hammer will always lie at or beyond the point C on the curved portion CD. If a concave downward form is assured, then at any contact point below C the hammer assembly will exert its weight obliquely, as in Figure 1. Therefore, the parts of the tonometer must be so assembled that the upper point of the plunger will never come below the point C throughout the normal use of the instrument.

Let E represent any other point of contact on the line AB. In order for the contact plane to be horizontal, the tangent to the hammer curve must be horizontal at the point E. Now let us allow the plunger to fall back to the position C. The point E in the elevated position of the hammer assembly corresponds to some point F in the "primary" position. Therefore, the tangent to the curve at F will make an angle with

Received for publication July 26, 1956.

This work was supported by a research grant from the Weinstock Fund.

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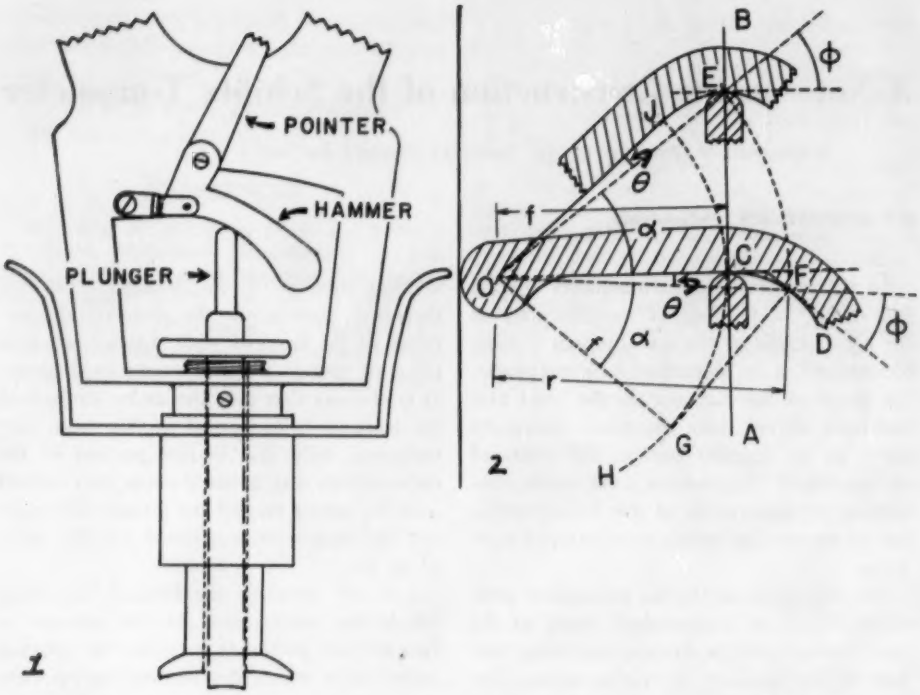

Fig. 1.—Lower portion of the conventional Schiøtz tonometer, with the weight of the hammer imparting a lateral thrust to the plunger.
Fig. 2.—The contact surfaces of the hammer assembly and the upper end of the plunger.

the radius vector OF exactly equal to the corresponding angle ϕ at E above.

In general, when a curve is described in terms of its polar coordinate equation in the form

$$r=g(\theta)$$

it is shown in the differential calculus [3] that the angle ϕ between the tangent at any point on the curve and the radius vector to that point is given by the formula

$$\tan \phi = r\, d\theta/dr$$

In the present case, it will be desirable to take the pole of the coordinate system at the fulcrum O. Let OC be the polar axis, and for convenience let us measure the angles θ downward from this axis (clockwise.) Then $r=OF=OE$, and the angle $\theta=COF=JOE$. The angle ϕ at F is equal to the angle ϕ at E, and this in turn is equal to the angle EOC (labeled α).

Let the fixed distance OC be called f. By the theorem of Pythagoras,

$$OE^2=OC^2+CE^2$$

or

$$CE^2=r^2-f^2$$

Consequently

$$\tan \phi = \tan \alpha = CE/OC = \sqrt{r^2-f^2}/f$$

Equating the two formulas for the tan ϕ, we therefore have

$$r\, d\theta/dr = \sqrt{r^2-f^2}/f$$

This may be considered as the differential equation for the desired curve expressed in polar coordinates.

In order to solve this differential equation, let us isolate $d\theta$ on one side of the equation and then make the substitution of variables $r=f \sec \alpha$. Employing standard formulas for differentiating and integrating trigonometric functions, we obtain

$$d\theta = dr\sqrt{r^2 - f^2}/rf$$
$$= (f \sec\alpha \tan\alpha\, d\alpha)(f \tan\alpha)(f \sec\alpha)f$$
$$= \tan^2\alpha\, d\alpha$$

Integrating

$$\int d\theta = \int \tan^2\alpha\, d\alpha$$
$$= \int (\sec^2\alpha - 1)d\alpha$$

Therefore,

$$\theta = \tan\alpha - \alpha$$

The constant of integration is zero, since when α is zero θ is also zero. Transposing the angle α and multiplying both sides of the equation by f, we obtain

$$f(\theta + \alpha) = f \tan\alpha$$

To interpret this result geometrically, let us now draw an arc of a circle with center at O and radius equal to OC, or f. Draw the radius OG so that angle FOG will equal α. Then triangles EOC and FOG will be congruent, since they have two sides and the included angle, respectively, equal. Therefore, OGF is a right angle, and GF is tangent to the arc CGH at G (and equal in length to CE).

Recalling that the length of a circular arc is equal to the radius multiplied by the central angle expressed in radian measure, we see that $f(\theta + \alpha)$ equals the length of an arc of a circle of radius f subtending an angle of $\theta + \alpha$ at the center of the circle. Such an arc is evidently GC. Similarly, an inspection of $f \tan\alpha$ shows that this term equals the line GF of the right triangle OGF (from $\tan\alpha = GF/OG = GF/f$).

Thus, we have obtained the result that GF, the tangent to the circle at the point G, is equal to the length of the arc GC. Since no assumption has been made as to the exact position of the point E, or of its counterpart point F, this conclusion will be true for any other point on the arc CD. We may, therefore, imagine a piece of string held taut against the circular arc HGC, attached to the circle at point H and tied to a movable pencil point at C. As the string is gradually unwound from the circle, we obtain the portion of the curve CD as the involute of the circle.[4]

Having established that a continuously horizontal contact implies that the hammer contact curve is an involute of the circle, we now inquire as to the plunger-to-pointer magnification ratio which will result. This is not difficult to determine, since the straight line CE, a representative displacement of the plunger, is equal in length to the segment GF, which in turn is equal to the arc GC, or to the arc CJ.

Thus, the vertical displacement CE is always equal to the linear displacement along the arc CJ, and this is proportional to the angular displacement COJ of the hammer and pointer. It follows, therefore, that the angular rotation of the pointer against its scale will always be proportional to the vertical displacement of the plunger, and hence a uniform scale is the only correct one.

The preceding discussion applies when the contact position remains at or above the point C. A very similar analysis leads to the involute curve, but convex downward, if the assumption is made that the contact takes place always at or below this point. However, the upper tip of the plunger cannot be allowed to move both above and below the level of the fulcrum point O if the advantages of the horizontal contact, i. e., decreased friction and uniform magnification, are to obtain.

With a convex downward hammer, the upper end of the plunger may be made a flat surface. This is not practical for the concave downward arrangement, but the substitution of a spherical or other rounded tip does not seem to imply any disadvantage.

Summary

The ideal shape for the contacting surface of the hammer assembly on the conventional Schiøtz tonometer has been investigated mathematically. Maintaining a horizontal surface of contact minimizes lateral frictional thrusts between the plunger and its shaft. It is shown that the only curve having this property to precision is the involute of a circle, either concave or convex downward. A secondary desirable feature is that the pointer rotation is always proportional to the plunger displacement.

This follows as a consequence of the geometrical properties of the involute curve.

York and Tabor Roads (41).

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Regenerative Processes in the Endothelium of the Cornea

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It was the purpose of this study to investigate the regeneration of the corneal endothelium under normal conditions and during wound healing.

A. Regeneration Under Normal Conditions

Cells which line the outer or inner surfaces of the body undergo gradual degenerative changes and are finally desquamated from the surface, while new cells are formed by mitosis or amitosis. Little is known about this process in the endothelium of the cornea.

Method.—Flat mounts of the corneal endothelium of 10 normal rabbit eyes were obtained by peeling off a very thin layer from the posterior corneal surface, including endothelium and Descemet's membrane. These preparations were about 50μ thick and were stained with hematoxylin only. The area of the posterior corneal surface thus obtained measured about 80 sq. mm. A grid in the eyepiece of the microscope was used for counting the endothelial cells under high magnification.

Results.—Evidence of amitotic cell division was found in each endothelium examined, but no mitosis could be seen (Figs. 1 and 2). The ratio of amitosis to normal endothelial cells averaged 1:8270. The individual variations of this ratio in the 10 rabbit eyes were considerable and are listed in the Table.

Received for publication July 23, 1956.

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It is known from observations in tissue culture work that amitotic cell divisions take about one hour (Macklin [1,2] and Lewis [3]). If we assume that the rate of growth is about the same at all times in a given endothelium, it is possible to calculate how long one endothelial cell might live and how long it might take until the entire endothelium is replaced. By dividing the number of endothelial cells n by the

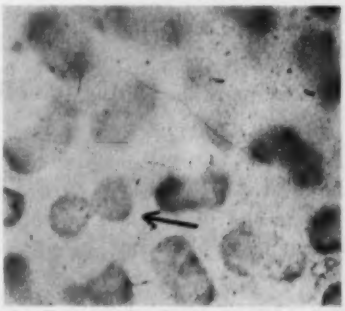
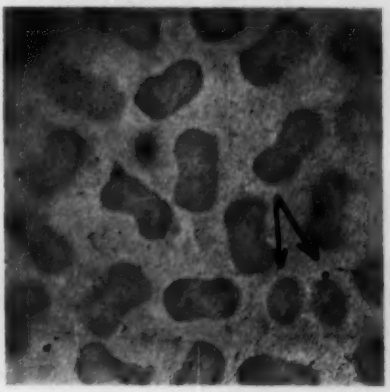


Fig. 1.—Regeneration in the normal endothelium of the cornea of the rabbit. Amitotic cell division (arrow); × 800.

Fig. 2.—Regeneration in the normal endothelium of the cornea of the rabbit. Amitotic cell division completed (arrow); × 800.



Amitotic Cell Division in Endothelium

Eye No.	Cells/Sq. Mm.	Ratio of Cell Divisions to Endothelial Cells	Life Span, Days
1	3,240	1: 9,818	409
2	3,092	1:10,307	429
3	3,185	1: 8,271	344
4	3,444	1:11,875	495
5	2,981	1: 6,084	254
6	3,352	1: 6,704	279
7	2,998	1: 5,250	219
8	3,222	1:10,394	433
9	3,259	1: 7,949	331
10	3,261	1: 6,035	251
Average	3,203	1: 8,270	344

number of cell divisions d the life span of endothelial cells s expressed in hours is obtained:

$$\frac{n}{d}=s$$

The average life span calculated for the 10 rabbit eyes amounted to 344 days, or almost 1 year.

This calculation is tentative, since too little is known about the actual duration of cell divisions and their possible variations in the corneal endothelium.

B. Regeneration During Wound Healing

Method.—The endothelium was stripped off the center of the posterior corneal surface by means of a blunt spatula, with sterile precautions. Particular care was taken not to rupture Descemet's membrane, since it was planned to study the changes in endothelial cells and their derivatives only. When Descemet's membrane is perforated cells from the corneal stroma may take part in the healing process.

The 20 rabbit eyes used for this study were enucleated at different intervals after the injury. Flat mounts of the endothelium were obtained by the method described above.

Results.—The denuded area was surrounded by a variety of cells 12 hours after the injury. The cells adjacent to the defect showed pseudopodium-like protoplasmic projections and were covering the defect by migration. Mitotic and amitotic cell divisions in all phases could be observed. A great number of small dark-staining nuclei

Fig. 3.—Cytology of endothelial wound healing. *M*, cell with giant nucleus. The small dark-staining nuclei among normal endothelial cells are derivatives of cell divisions. Twenty-four hours after injury; reduced from mag. × 800.

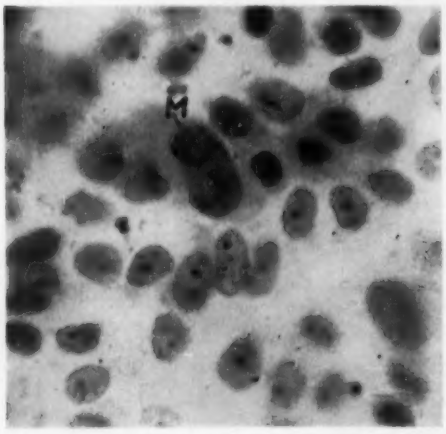
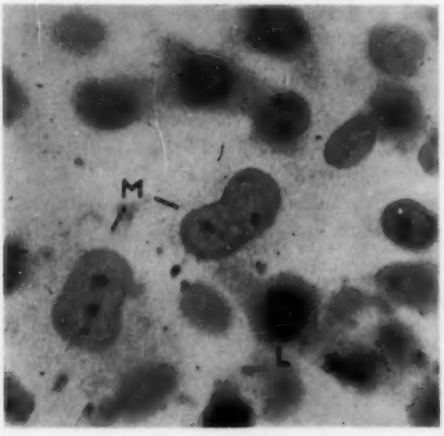


Fig. 4.—Cytology of endothelial wound healing. *M*, cells with giant nuclei. *L*, lymphocyte. Twenty-four hours after injury; reduced from mag. × 800.



represented the young cells derived from these divisions.

The number of mitoses was greatest during the 24- to 36-hour period. While mitosis had practically disappeared from the injured area after five days, amitoses were still present after two weeks. The denuded area was covered in most cases after four days.

From the very beginning cells with very large nuclei were present in a considerable number (Figs. 3 and 4). They had a very delicate nuclear membrane and clearly visible nucleoli.

It was surprising to find many lymphocytes among the cells mentioned, since no inflammatory reaction was observed clinically and no polymorphonuclear leukocytes could be seen in our specimens.

Comment

Cogan stated [4] that mitoses are never seen in normal endothelium. It appears that the present results confirm this statement. It is felt that amitosis is the method of regeneration of the corneal endothelium of the rabbit under normal conditions and that mitotic cell divisions occur under unusual circumstances only.

Brückner [5] and Verrey,[6] in their studies on the cytology of the aqueous, found desquamated endothelial cells. This together with our observation of occasional vacuolated cells in the normal endothelium proves that there is a need for cell regeneration.

Nagano,[7] Stocker,[8] and Fuks [9] reported cytological details of endothelial wound healing. Only Nagano mentioned the cells with the large nuclei and gave excellent illustrations of them. However, no interpretation of the nature of these cells has been offered. It is conceivable that these cells are macrophages which derive from endothelial cells by metaplasia under the stimulus of the injury. It is further thought that the lymphocytes (microphages) might also originate from endothelial cells by metaplasia.

Most authorities agree that the corneal endothelium originates from the mesoderm. Several observations (ingestion of vital stains, participation in connective tissue formation) suggest that the corneal endothelium is part of the reticuloendothelial system, which usually gives origin to macrophages and microphages.

This hypothesis is further supported by the observation of Lippman and Brückner,[10] who found lymphocytes after irritation of the anterior segment of the globe in aleukocytotic animals.

Summary

The regeneration of the corneal endothelium of the rabbit under normal conditions occurs by amitosis. A calculation of the life span of endothelial cells was attempted. It was felt that the cells with large nuclei which appear during wound healing of the corneal endothelium are macrophages originating from endothelial cells by metaplasia.

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Radioactive Phosphorus in Differential Diagnosis of Ocular Tumors

Special Reference to Results of University of Michigan Study, July 1954-May 1956

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Introduction

One of the most difficult problems in ophthalmology is the differential diagnosis between benign and malignant intraocular lesions. In addition to the usual difficulties offered in such a diagnosis in any body location, the eye presents the complicating feature that many of its lesions cannot be biopsied without irretrievable damage to the function of the organ.

Since the advent of the application of radioisotopes to clinical practice there has been the great hope that the isotopes could become an important aid in diagnosis and treatment of malignancy. In ophthalmology recent years of experience have established radioactive phosphorus as a most important but not absolute test for malignancy.

Background

Terner, Leopold, and Eisenberg [1] have written an excellent review article. For the background of the use of P^{32} in medicine generally or ophthalmology specifically this article is highly recommended.

Many authors [2-7] have written concerning the excessive uptake of P^{32} by malignant tissue in the eye.

Received for publication July 30, 1956.

This study was supported by the Ophthalmological Research Fund of the University of Michigan.

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Presented at the Scientific Session following the Third National Cancer Conference on Thursday, June 7, 1956, Ann Arbor, Mich.

Radiophosphorus, rather than other isotopes, has evolved as the isotope of choice in this area predominantly because of the type of radiation emitted by phosphorus. The radiation is a beta radiation, thus approximately 8 mm. of tissue will stop effectively all of the radiation emitted and there will be no masking effect from more remote tissues. For example, a counter on the cornea near an iris malignancy would receive the beta emission of the malignancy because of the proximity of the iris to the counting device. The normal beta emission from uptake of the normal choroid far back of the iris would not reach the counter and obscure the results, as the choroid would be too far from the counter. On the other hand, if more penetrating rays, such as the gamma rays of I^{131}, were utilized, radiation from the iris lesion, normal choroid, and other tissues would reach the counter and thus obscure the differential uptake of isotope by the iris.[4]

From the above comments one can see that the technique of counting could be most important—position of counter and inclination of counter can be of critical import. Bettman and Fellows [8] have written concerning the physiological, anatomical, and physical difficulties which may be encountered in counting P^{32} around the eye.

There is general agreement in the literature that the closer one can place a counting device to the suspected area the more accurate will be the result. Consequently, the test seems to be on a sounder basis for the more easily available anterior lesions than it is for the remote posterior lesions. To

count the P^{32} emission of anterior lesions a small Geiger-Muller tube with an end-window placed directly over the lesion is utilized. For posterior counting, curved Geiger-Muller tubes [9,10] and curved scintillation counters [11] have been designed.

Technique

When the question of intraocular or adnexal malignancy arises, the usual adult patient is given 500μc of P^{32} intravenously. For children the dose is adjusted downward on a weight basis.

Originally in our series a count was done immediately, then in one hour, then in four days. We soon came to realize that the only reproducible results were obtained in the delayed counts, and most recently we have felt that a single evaluation at about the 48-hour postinjection time gives us our most significant results. It is important to recognize the fact that many nonmalignant lesions a few hours after injection will give an excessive count which will fall when checked at a more delayed time.

At 48 hours, to count an anterior lesion the patient is requested to lie on an ordinary examining table on his back as comfortably as possible. The eyes are anesthetized with 0.5% tetracaine (Pontocaine) hydrochloride drops, and, utilizing a small end-window Geiger-Muller tube, with careful apposition, counts are made directly on the eye. By requesting the patient to fixate gaze in desired direction counts may be made with the anterior probe probably as far back as the equator of the globe. The area of suspicion will of course determine the exact placement of the counter, but as a general rule one attempts to count in all four quadrants of the globe.

There must be a great effort made to standardize the application of the counter regarding position on the eye and inclination, or else variable results will be noted. We have found that it is wise to avoid placement of the counter over rectus muscle masses, as they tend to elevate the count.

Our most important comments on the actual counting are those related to the variability of counts from one moment to the next. For reasons that we cannot explain counts may vary rather enormously under what is apparently standard counting conditions. Thus enough counts (and this will vary with the individual case) must be done so that a definite trend for the individual patient can be established. This can be quite time-consuming.

We also feel that a standard must be created for each patient as an individual person. In some cases the entire affected eye will show an excess over the nonaffected eye and thus the nonaffected eye becomes the standard. In other cases, particularly with small lesions such as localized iris lesions, the affected area may show an excess over its own eye and thus the remainder of the same eye becomes the standard.

In cases where there is suspected bilateral disease, or the patient is monocular, it has been suggested that a neutral tissue such as the ear lobe be used as control area. In our series we have not had recourse to this device, and I should think that one would have to be cautious if one did so, because very high uptakes may be recorded from such normal vascular tissues as the tongue.

We have used as a criterion of positivity a repeatable, definite excess uptake of 30% in 48 hours.

Terner, Leopold, and Eisenberg [1] take readings at 1 and 24 hours. They consider any initial count above 30% as significant, but they do not make a positive diagnosis unless the 24-hour count is greater than the 1-hour count. In a recent communication Fry [12] has suggested that less than 30% excess uptake in iris lesions is significant.

I would stress again that in our experience the important feature of counting is to individualize each patient concerning areas of counting and proper control areas and above all to do enough counts so that an unquestioned trend may be noted.

The eyes are irritated very little with this procedure. We routinely instill a drop of sulfacetamide U. S. P. (Sulamyd) 30% at the end of the test. General anesthetic is suggested for young children.

Posterior counts are considered as operative procedures. These are again done at 48 hours. The patient is prepared and draped in the usual operative fashion. With use of sterile technique, orbicularis oculi akinesia is obtained with injected 1% lidocaine (Xylocaine). Topical tetracaine is used as well. A small incision is made in the conjunctiva and Tenon's capsule, and a curved posterior counter is slid along the sclera to the suspected area and counts are made. Usually, from this one incision another area may be counted as a control. If necessary, an additional incision may be utilized to open a control area. The incision is closed with 000000 mild chromic absorbable surgical (gut) sutures; sulfacetamide 30% is instilled, and the eye is padded. For a few days following, sulfacetamide and compresses are advised. We have had no complications in 13 posterior countings.

In attempting to evaluate an adnexal lesion one places the counter as close to the lesion as possible and again checks with control areas. Some studies have been done on lid lesions elsewhere, but we do not recommend isotope study for any lesion which may be safely biopsied or excised.

Results

Eighty isotope countings were done without incident. Of these 80 countings, 3 were on the same patients counted twice some months apart, with the same results. Thirteen posterior counts were done.

Twenty-four cases have been pathologically followed, and it is only these cases that I shall discuss, as they give the full information which is required to evaluate the findings. This, of course, weights the report in one respect, as it is only the most suspicious lesions which come to operation. However, in view of the results which follow, and particularly the negative isotope findings in pathologically proved malignancy, I feel that the weighted report is justified.

Comments

(1) Even in a group weighted toward operation one notes the false negatives—Cases 2, 7, and 9.

(2) Particular reference is made to Case 9, where with both anterior and anterior-posterior counts, done 10 months apart, negative results were noted in a case of malignancy. The referring physician con-

Data from Twenty-Four Pathologically Proved Cases

Case	Clinical Diagnosis	Pathological Diagnosis	Isotope Report*
1	Malignant melanoma, anterior choroid	Malignant melanoma	Positive
2	Malignant melanoma, anterior choroid	Malignant melanoma	Negative
3	Chronic inflammation, intraocular	Chronic granuloma	Negative
4	Malignant melanoma, iris	Iris nevus (benign)	Negative
5	Chronic inflammation, intraocular	Chronic inflammation	Negative
6	? malignancy, intraocular	Chronic inflammation	Negative
7	Neuroblastoma, orbit	Neuroblastoma, orbit (metastatic)	Negative
8	Retinoblastoma	Retrolental fibroplasia	Negative
9	Pigmented lesion, posterior choroid	Malignant melanoma	Negative (anterior and anterior-posterior counts 10 mo. apart both negative)
10	Malignant melanoma, choroid	Malignant melanoma	Negative with anterior count, positive with posterior count
11	Chronic inflammation, intraocular	Chronic inflammation	Negative (anterior-posterior count)
12	Malignant melanoma, anterior choroid	Malignant melanoma	Positive
13	Malignant melanoma, ciliary body	Malignant melanoma	Positive
14	Malignant melanoma, choroid	Malignant melanoma	Positive
15	Proptosis O. S.	Lipoma	Negative
16	Lacrimal gland tumor	Chronic inflammation	Negative
17	Malignant melanoma, iris	Malignant melanoma	Positive
18	Chronic inflammation, intraocular	Chronic inflammation	Negative (anterior and anterior-posterior counts 5 mo. apart both negative)
19	Malignant melanoma, choroid	Malignant melanoma	Positive (anterior-posterior count)
20	Lacrimal gland neoplasm	Benign mixed tumor	Negative
21	? malignant melanoma, iris	Post-traumatic iris degeneration	Negative
22	Malignant melanoma, choroid	Malignant melanoma	Positive (anterior and posterior count)
23	Malignant melanoma, choroid	Malignant melanoma	Positive
24	Malignant melanoma, with extraocular extension	Cavernous hemangioma orbit	Negative

* Unless specifically stated, the count was anterior count alone.

firmed the presence of the malignancy after enucleation.

(3) Case 10, negative with an anterior count, positive with posterior count. It is to be noted also that the literature on this subject has reported false positive results as well, particularly in inflammatory disease.

(4) Case 17 indicates how individualization of counts must be done. This iris lesion had 18% to 22% greater uptake than the control area in the other eye. However, the lesion had 38% excessive uptake over its own eye background. The control area in the opposite eye was 5% over its own background. The results of the study were correctly reported as positive.

Conclusions

The differential uptake of P^{32} by malignant ocular tissue can be a definite adjunct in making the difficult diagnosis of ocular malignancy. However, the entire clinical picture and judgment is the final determining criterion and the test is considered as an adjunct only.

In view of the lack of knowledge of the long-term results of body radiation, the test should be used with caution, in indicated cases only.

Summary

The results of isotope countings of 24 pathologically proved cases emanating from a series of 80 radioactive phosphorus determinations around the eye are reported.

Techniques of anterior and posterior counts are described.

Stress is laid upon the necessity for individualization of criteria of positivity.

Three false negative reports are noted.

Conservatism in the use of the test is suggested.

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Congenital Coloboma Associated with Cystic Degeneration of the Ciliary Body

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Coloboma of the lens is often associated with colobomata of the uveal tract in the inferior quadrant. A case of coloboma, nasally situated, is herein reported which is believed to have developed as a result of congenital cystic formations in the ciliary processes pressing upon the equator of the lens.

Report of a Case

A white girl was first seen at the age of 6 years because of a concomitant convergent strabismus. The left eye was normal in all respects, with the corrected vision 20/20. Vision in the right eye was limited to counting fingers at one foot.

Thorough examination of the right eye after maximal dilatation revealed these findings: (1) strands of persistent pupillary membranes; (2) an irregular coloboma of the lens equator on the nasal side through which, with pupil dilated, the normal zonular fibers could be seen bridging the gap between the coloboma line and the ciliary body; (3) three globular enlargements of the ciliary processes visible behind the pupillary rim of the iris; (4) "finger print"-like pigment deposits on the posterior capsule of the lens and anterior surface of the hyaloid, suggesting previous larger masses of pigment which must have receded, and (5) posterior polar cataract.

Transillumination of the globe showed the cystic character of the ciliary masses. Visualization of the fundus revealed two healed patches of choroiditis temporal to the optic disc.

The concomitant squint was corrected by surgery, and the patient has been regularly followed for the past 22 years, the last examination being on April 6, 1956.

Except for some increase in the opacity of the lens, there has been no change in the appearance of the coloboma, in the cystic masses in the ciliary body, or in the "finger print" deposits of pigment.

Comment

An analysis of this case from an embryological viewpoint suggests that the cystic masses in the ciliary body "stood in the way" of the normal development of the lens along its nasal edge, thus resulting in a coloboma. As these cysts receded, they left their "finger print" impressions of pigment deposits on the posterior lens capsule and on the anterior surface of the hyaloid.

The interesting aspects of this case are illustrated in the accompanying drawing.

Submitted for publication June 21, 1956.

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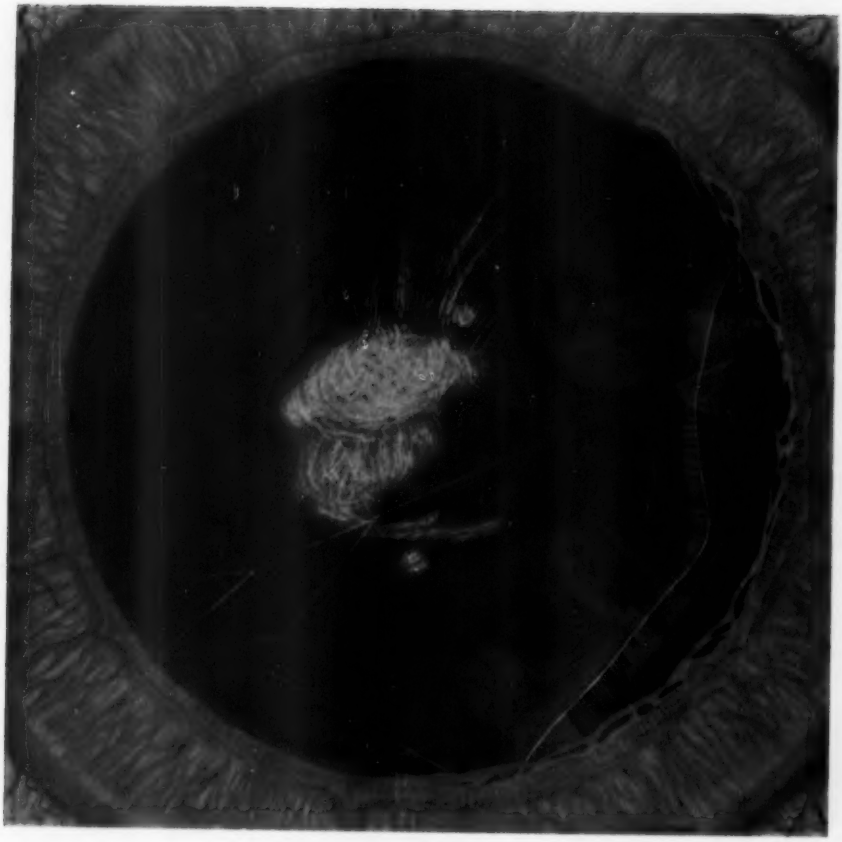


Anomalous congenital coloboma of the lens; slit-lamp study.

Chordomas of Ocular Interest

CHARLES DYSON, M.D., London, Ont., Canada

The existence of tumors derived from the notochord has been known for more than 100 years. In 1857, Virchow [1] noted the presence of gelatinous excrescences upon the clivus of Blumenbach and, mistakenly assuming them to be of cartilaginous origin, called them "ecchordoses physaliphora." In 1858, Müller [2] suggested the theory of notochordal genesis, which was supported by Ribbert,[3] who produced the histological picture of noninvasive chordal tissue by puncturing the nuclei pulposi of rabbits. Ribbert also suggested the now commonly accepted terminology of chordoma.

Some discussion of the embryology of the notochord is an essential preface to the description of chordomas. The notochord, a primitive axial supporting structure of the embryo, undergoes successively greater regression as it ascends the phylogenetic ladder. In Amphioxus it persists as the sole supporting column, but the only vestiges ordinarily found in humans are in the nuclei pulposi. It is considered by Arey [4] to be of mesodermal origin, although Baxter [5] believes that it arises from entoderm. At the height of its development, it passes from the buccopharyngeal membrane caudally, pursuing a curving, tortuous course along the base of the skull, traversing the apical odontoid ligament, the anterior atlas, and all the vertebral bodies. Its regression seems to be determined by its envelopment in the developing cartilage and bone, for it is in areas in which this process does not occur readily that clinical tumors develop. Thus, in the base of the skull, chordomas are found usually arising from the dorsum sellae, the clivus, or the epipharynx. Although chordomas have been described along virtually all points of the notochordal path, there is a definite predilection for the caudal and cephalic extremities. About one-third of reported cases are intracranial,[6] and this discussion will be restricted principally to those intracranial chordomas which show signs and symptoms of ocular interest. The literature pertaining to chordomas in general has been well reviewed by Stewart and Morin,[7] Bailey and Bagdasar,[8] Hass,[9] and Mabrey.[10]

The small tumors first noted by Virchow were undoubtedly the "benign" form of chordoma. They are most commonly found on the clivus as a small soft tumor, often attached to the underlying bone by a fragile pedicle through a dural defect. They represent merely ectopic chordal rests and have an incidence of 1.5% to 2% (Ribbert [3]; Stewart and Burrow [11]). However, Willis [12] found them in only 5 of 1000 necropsies in which they were specifically sought. Whether these may assume an invasive form and become malignant is speculative.

The malignant types which cause ocular signs and symptoms are nearly always those arising from the cephalic end of the notochord, particularly in the region of the clivus, or the dorsum sellae. These tumors have three general directions of growth—anteriorly toward the sella turcica, posteriorly toward the foramen magnum, or ventrally to the postpharyngeal space. The latter group appear as retropharyngeal tumors, and they are especially susceptible to biopsy diagnosis.

The clinical picture is determined by the geography of the lesion. Chordomas have a marked tendency to impair function of

Received for publication June 18, 1956.

Read before the joint meeting of the British Medical Association, the Canadian Medical Association, and the Ontario Medical Association in Toronto, Ont., Canada, June 21, 1955.

cranial nerves and to invade bone. Cranial nerve involvement is usually unilateral at first. Palsies of extraocular muscles or pupillary anomalies may appear. Cutaneous areas supplied with sensory nerves by the trigeminal nerve may exhibit hyperesthesia, paresthesia, or anesthesia. Corneal anesthesia may be present. Facial nerve palsies are less common, and anosmia is rare. Those chordomas which extend anteriorly, or those originating near the sella, may invade this structure to cause bone erosion and chiasmal pressure, resulting in changes in central vision and fields suggesting primary pituitary tumors. However, signs of pituitary dysfunction are rare in such instances,[9] although Adson [13] and Freeman [14] have each reported cases with endocrine abnormalities in association with chordomas. Möller [15] described a chordoma of the clivus which had invaded the prechiasmal portion of the optic nerves, causing optic atrophy and, secondarily, a Bjerrum scotoma typical of glaucoma, although no ocular hypertension could be found.

Not only may continued growth anteriorly result in destructive effects upon the sella turcica but the sphenoid and ethmoid sinuses may also be invaded. Intraorbital extension and proptosis have been noted by several authors, such as Roche,[16] Argaud,[17] and Zeitlin and Levinson.[18]

Increased intracranial pressure and papilledema are found in many clinical descriptions. An interesting case is that described by Schneegans and Mandigas,[19] in which a chordoma of the spheno-occipital region compressed the aqueduct of Sylvius to cause a rapidly progressive hydrocephalus in a 5-month-old child.

Chordomas are usually only locally invasive, with little tendency to metastasize. The case reported by Schneegans and Mandigas [19] had metastasized to heart and lung and was unusual in that it represented a case of intracranial chordoma with metastases. Most metastases are associated with primary sacral or vertebral tumors. The paucity of intracranial chordomas with metastases may reflect their earlier exodus by reason of local pressure effects.

Clinical diagnosis is difficult. The protean characteristics of signs and symptoms, associated with a meandering, invasive spread along the base of the skull, usually results in a puzzling clinical picture which is rarely diagnosed before operation and biopsy.

Radiologic investigation is usually helpful. X-ray evidence of destruction of bone at the clivus and spheno-occipital junction is found in all clival chordomas. The dorsum sellae, posterior clinoids, and floor of the sella are usually eroded by chordomas which arise or extend more anteriorly. Encephalography and ventriculography may show upward displacement of the third ventricle and posterior displacement of the aqueduct and fourth ventricle. Some clival tumors may be outlined by gas in the basal cisterns. Occasionally, bony sequestra may be visualized.[20]

The age and sex of the patient are of interest, as most chordomas occur in middle-aged men. The average age in the group studied by Hass [9] was 36. However, both sexes, and all ages, may be affected.

From the viewpoint of the ophthalmologist, chordomas arising from the cephalic extremity of the notochord must be differentiated particularly from tumors originating in and around the pituitary fossa and optic chiasm. They may be confused with adenomas or carcinomas of the pituitary gland, and, indeed, most case reports of chordomas in this area note that they were diagnosed clinically as pituitary tumors. Craniopharyngiomas, meningiomas of the parasellar regions and of the olfactory groove, and gliomas of the optic chiasm must be considered. Clival chordomas are more prone to cause internal and external ophthalmoplegias and may simulate pontine gliomas, meningiomas, and accoustic neuromas.

The gross appearance of a chordoma is usually that of a reddish-gray smooth-surfaced encapsulated mass, divided into lobules by connective tissue septa. Areas of hemor-

rhage and necrosis may be seen. These tumors are usually extradural, often invade bone, and may contain bony sequestra which they have enveloped. If the capsule is opened, a slimy, mucinous substance is seen.

Microscopically, the typical picture is that of cords of large epithelial-type cells, surrounded by a mucinous matrix. The nuclei and cytoplasm are vacuolated and contain a substance staining with Best's glycogen stain. Bruce and Mekie [21] have described how the varying cytology of chordomas may recapitulate the histogenesis of the notochord, which evolves through early stages of solid, supporting cells to vacuolated forms and then to cells with pyknotic nuclei which have extruded their intracellular mucin. Thus, the chordomas comprised of young, solid cells are considered most malignant, and the ones containing fewer cells and abundant mucinous matrix are thought to be less malignant.

The treatment of intracranial chordomas is usually surgical, but complete removal is impossible in almost all cases because of the inaccessibility and invasiveness of the tumors, and the involvement of cranial nerves.

Chordomas are not usually radiosensitive. Friedman,[22] however, described the apparent eradication and restoration of normal radiologic contour of a lumbar vertebra following the treatment of a chordoma of the vertebral body with 2,000,000 volt therapy. Andrews [23] noted the rapid regression, after radiotherapy, of a biopsy-proved chordoma of the spheno-occipital region with nasopharyngeal extension. Relatively small doses were directed at the pituitary region and to the site of the pharyngeal spread. In both cases, the follow-up period is not long enough to be conclusive. The general experience with radiotherapy has been disappointing in most reported cases.

The prognosis of chordoma is bad. Those arising from the base of the skull and giving rise to ocular signs are almost invariably lethal if followed sufficiently long. Hass [9] states that the average duration of life in this type is three years from the onset of symptoms. As mentioned earlier, there is only very slight tendency for these tumors to metastasize.

Report of a Case

A 57-year-old white man first complained of double vision and occipital pain on Sept. 21, 1951. At this time, visual acuity with correction was reported as 20/20 in each eye. Visual fields were normal, but the right lateral rectus was paretic.

Four months later, a macular degeneration was noted in the right eye, reducing central vision to 20/200, and the right optic disc was noted to be noticeably atrophic on the temporal side.

On June 19, 1952, he complained of a severe increasing right-sided supraorbital pain. He now denied light perception in the right eye, and the diplopia, of course, was not present. Both the right lateral rectus and the right superior rectus were now paralyzed. The right pupil was fixed and

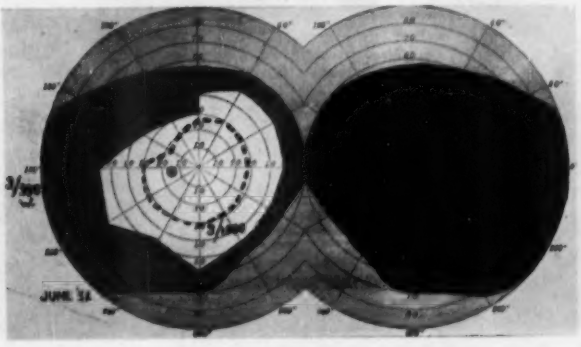


Figure 1

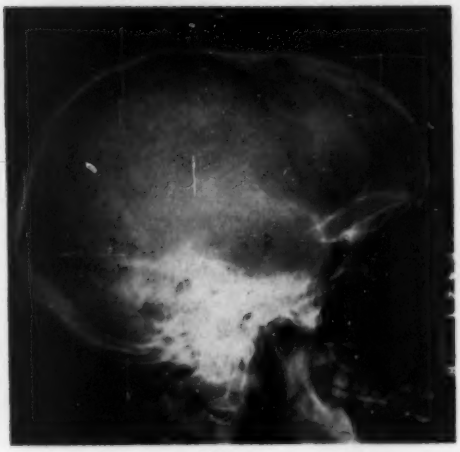


Figure 2

dilated. Fields of vision (Fig. 1) revealed an early upper temporal quadrantic defect. Skull plates (Fig. 2) showed enlargement of the sella turcia with destruction of the floor and posterior clinoids. Slight enlargement of the right optic foramen was also noted.

Although no pituitary dysfunction was evident, the clinical diagnosis of pituitary tumor was made, and cisternal air studies seemed to confirm this. Surgical exploration was undertaken on July 8, 1952.

A tumor was found presenting under both optic nerves. The right nerve was displaced upward and flattened by the tumor pressing it against the superior border of the optic foramen. This was thought to be the cause of the foraminal enlargement noted radiologically. The capsule of the tumor was opened between the optic nerves, and the contents were evacuated with suction and curettage. Microscopic examination showed the typical cytological picture of chordoma (Figs. 3 and 4).

After this operation, the patient noticed a return of light perception in the right eye.

Further therapy consisted of irradiation with Co^{60} (3500 r, given over a three-week period, through a 4 cm. circle). Shortly after this treatment, a rather rapid decrease in left central vision and peripheral field was evident. Reoperation in February, 1953, showed new tumor growth, and a large blood clot found within the tumor capsule at this time raised the question of possible radiation necrosis and hemorrhage.

After the second operation there was slight recovery of left central vision and field. Pain over the right trigeminal distribution persisted. Death occurred on April 1, 1953, from bronchopneumonia.

At necropsy a tumor was found projecting from the hypophyseal fossa, extending extradurally to the right and involving the greater wing of the sphenoid, the orbital plate of the frontal bone, the cribriform

Figure 3

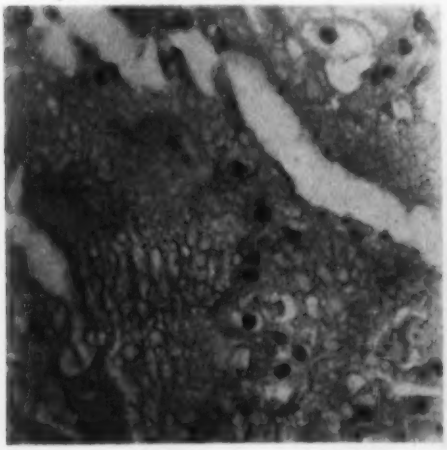
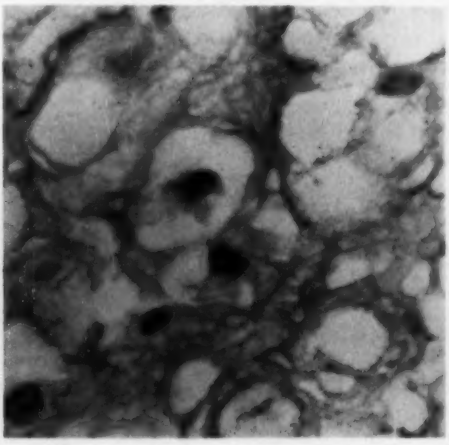


Figure 4



plate, and the crista galli. The tumor had also involved the posterior clinoids, the dorsum sellae, and the optic chiasm. There were no metastases. Microscopic sections again showed the typical picture of chordoma.

Thus, the case was that of a middle-aged man who experienced diplopia, unilateral visual loss, and contralateral field changes associated with chiasmal pressure and whose skull films showed bony changes in the sella turcica and one optic foramen. This clinical picture was caused by a chordoma arising within the dorsum sellae.

Summary

A general outline of the origin, clinical picture, treatment, and prognosis is given of those malignant intracranial chordomas which cause changes within the ocular sensory and motor spheres. A case of this type is described.

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Pediatric Anesthesia

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Anesthesia in the pediatric patient may produce severe psychic trauma. While attempting to avoid this problem, one must maintain an optimum physiologic state as well as provide satisfactory operating conditions. Fundamental principles of pediatric anesthesia and mechanical aids in administration of the anesthetic not only are of interest but are essential for the safety of the child. These factors will be discussed.

Premedication

Important considerations in premedicating infants and children are age, physical status, and psychic state. Properly administered and timed, premedication will alleviate apprehension, reduce reflex hyperactivity, diminish salivary and bronchial secretions, and produce a degree of basal narcosis. The anesthetic risk and the volume of anesthetic agent necessary to maintain the desired operative state are reduced in the properly premedicated patient.

Psychic trauma is avoided if preoperatively the patient's confidence is obtained and he or she is informed in a simple and truthful manner of events leading up to the time of unconsciousness. Of equal importance are adequate premedication given one to one and a half hours preoperatively and a nontraumatic induction.

Patients ranging from birth to 4 or 5 months in age have a low metabolic rate and should not be depressed with opiates or barbiturates. They are not a problem from the standpoint of psychic trauma and therefore only atropine or scopolamine is given preoperatively. These drugs decrease reflex hyperactivity and salivary and bronchial secretions.

In patients from 5 months to 3 or 4 years, pentobarbital sodium, 6.5 mg. per kilogram, is given in a retention enema 40 to 60 minutes preoperatively. Intramuscular secobarbital sodium, 5.5 mg. per kilogram, may be used in place of the rectal pentobarbital. The dosage of either drug is varied to compensate for abnormal physical or mental activity. The patient is to be in a state of light hypnosis from which he may be easily aroused but without excitement (Fig. 1*A*). This is preferred to a poorly premedicated patient as illustrated in Figure 1*B*.

In children over 5 years of age, pentobarbital can usually be given orally. An opiate, meperidine or morphine, is given with a belladonna drug. The majority of these patients receive either thiopental and nitrous oxide or cyclopropane.

Pressure on the eyeball may initiate the oculocardiac reflex, which is a parasympathetic reflex. The afferent portion is by the oculomotor nerve, and the efferent portion is by the vagus nerve to produce bradycardia. The occurrence of this reflex during eye surgery is usually prevented by adequate premedication with a belladonna drug and the instillation of a topical anesthetic agent such as tetracaine or cocaine into the eye during the induction phase.

Induction

A mask is never placed directly on the patient's face while he is conscious, and the patient is never vigorously restrained. The Yankhauer (open drop) ether mask has been abandoned because there is up to 250 cc. of dead space under the average mask.[1] This leads to carbon dioxide accumulation. In preference to the Yankhauer mask, a

Received for publication June 11, 1956.

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Presented at the Annual Meeting of the Pacific Coast Oto-Ophthalamological Society, Phoenix, Ariz., April, 1956.

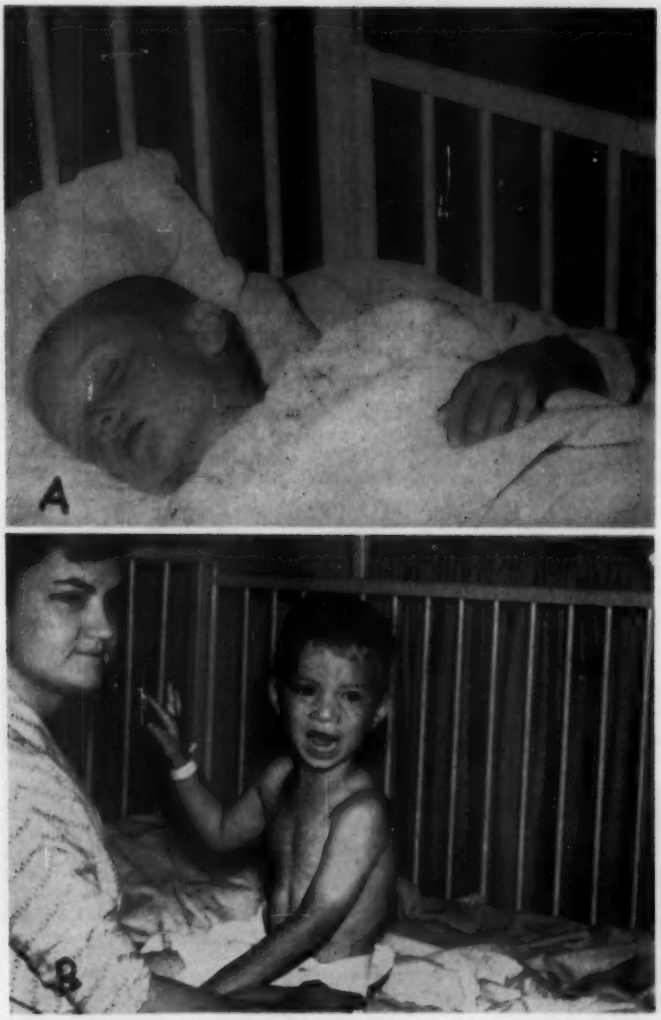

Fig. 1.—*A*, patient adequately premedicated. *B*, patient poorly premedicated.

Digby Leigh or Steven-Slater valve and bag is used. No rebreathing is present, and excessive carbon dioxide accumulation is avoided (Fig. 2).

In small infants, respiration and cardiac rate and rhythm are heard through a precordial stethoscope with a molded earpiece (Fig. 3). Continuous evaluation of these vital functions is of major importance and is accurately made by this method. Any cardiorespiratory changes are immediately known, and this may be of lifesaving importance in case of cardiac arrest. Routine blood pressure determinations are unsatisfactory in this group. Induction with cyclopropane and ether followed by ether maintenance is the anesthetic of choice. The excitement stage is greatly shortened or eliminated by the use of cyclopropane.

In the patient inadequately premedicated and over one year of age, induction is partly carried out with the patient sitting in the anesthetist's lap. The child is shown the "sleepy rabbit,"[2] through which cyclopro-

Fig. 2.—Induction with a Fink modification of Digby Leigh valve and bag, allowing assisted or controlled respirations when necessary.

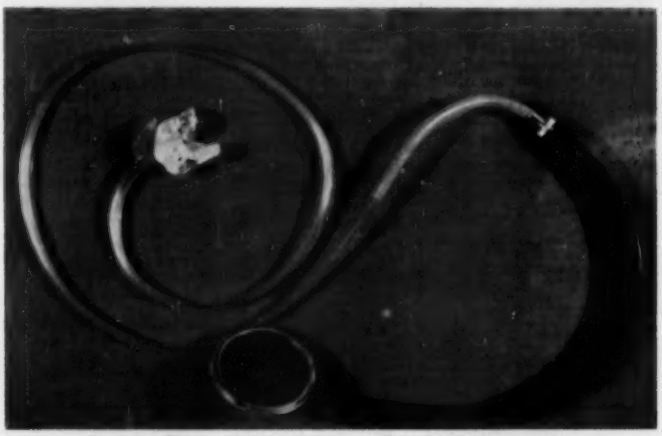

Fig. 3.—Precordial stethoscope with a molded earpiece.

pane or nitrous oxide is flowing (Fig. 4). However, this toy is not the answer to all induction problems. Some patients may react negatively toward the toy, in which instance it is removed and only the tubing carrying the anesthetic agent is used. The toy and the Stephen-Slater or Digby Leigh valve and bag are the two simple devices which have proved very satisfactory for induction in infants.

Children over 4 years of age adequately premedicated and psychologically prepared may receive intravenous thiopental as an induction agent. However, one must be fully cognizant of its respiratory depressant effects.

Techniques

Respiratory dead space and resistance to breathing must be minimal if one is to maintain a normal physiologic state. It is our feeling that a nonrebreathing technique is the technique of choice. This is best accomplished by the use of a Digby Leigh valve and bag. A minimal amount of resistance to respiration is produced by the inspiratory and expiratory valves. The Fink modification of the Digby Leigh valve[3] (Fig. 5) enables one to assist or control respiration without difficulty, since positive pressure on the bag automatically closes the expiratory valve. By use of this tech-

Fig. 4.—Anesthesia induction with the "sleepy rabbit" in an inadequately premedicated patient. Note absence of physical restraint.

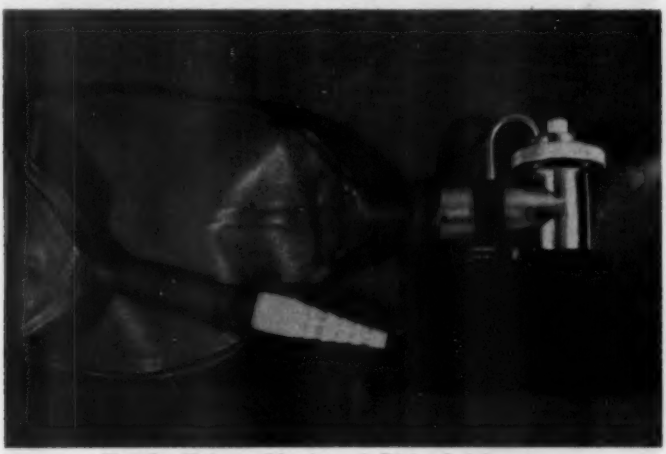

Fig. 5.—Fink modification of Digby Leigh valve.

nique a fresh mixture of gases is delivered with each respiration, thus reducing the problem of carbon dioxide retention.

Patients requiring surgery about the eye deserve endotracheal anesthesia except in rare instances. The main advantages of this technique are improved working conditions for the surgeon, controlled or assisted respirations when necessary, prevention of aspiration of fluids or tissues, reduction of

dead space, and better elimination of carbon dioxide.

Endotracheal intubation is done with particular care in infants. Before intubation they are in the second plane of surgical anesthesia, to eliminate laryngeal spasm and subsequent trauma to the vocal cords. In the infant, the average diameter of the tracheal orifice at the cricoid ring is 4 mm. One millimeter of edema at this level decreases the cross sectional area 75%, as compared with 19% in the adult, whose tracheal orifice at this same level is 20 mm.[4] The newborn infant's trachea is only 4.5 cm. in length, and the endotracheal tube must not be inserted too far or it will enter the right main stem bronchus (Fig. 6). This is easily detected by failure of expansion of the left chest and by absence of respiratory sounds through the precordial stethoscope.

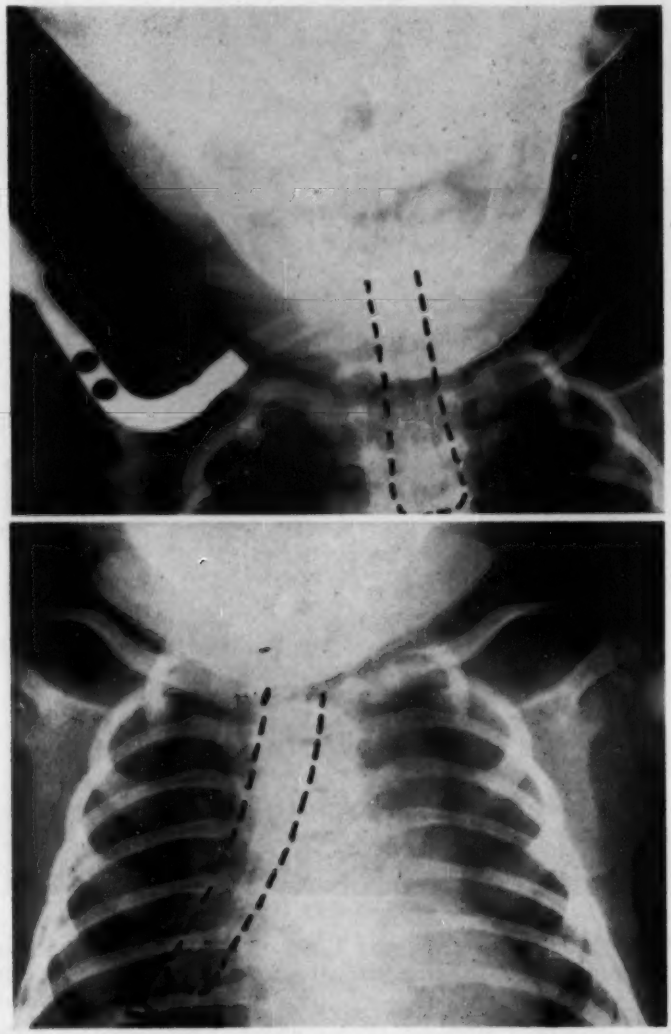

Fig. 6.—*A*, x-ray showing properly placed endotracheal tube. *B*, x-ray showing endotracheal tube in the right main stem bronchus.

Fig. 7.—Patient with oral endotracheal tube and Turnbull connector.

Fig. 8.—Patient draped ready for surgery. Note surgical field free of mechanical obstruction.

Turnbull connectors are used, resulting in an open endotracheal technique (Fig. 7). A fresh mixture of gases is delivered with each respiration, and the apertures on the sides of the connector allow free exhalation and the escape of gases over and above the patient's tidal volume. The only resistance to respiration is that produced by the endotracheal tube. Respiratory assistance is accomplished by alternate occlusion of the

apertures in the connector. The degree of pulmonary aeration produced is easily determined with the precordial stethoscope. This technique (open endotracheal) has the added advantage of placing the anesthetist at a distance, with no reservoir bag or other cumbersome equipment obstructing the surgical area (Fig. 8). Transnasal as well as oral intubations can be done and still leave the operative field free for the execution of the surgical procedure to the best of one's ability.

The endotracheal tube is kept free of tracheobronchial secretions. During tracheobronchial aspiration in infants, the respiratory mucosa may easily be injured and forceful suction may produce partial atelectasis. Aspirations are therefore done with a De Lee mucous trap and a small plastic catheter, with the anesthetist supplying the suction by mouth (Fig. 9).

A semiclosed circle system technique may be employed in children 4 or 5 years of age and older. When this technique is used, a slow continuous drip of 0.1% succinylcholine chloride allows a lighter plane of anesthesia with complete relaxation of the ocular muscles.

Maintenance and Supportive Therapy

In older children, a blood pressure cuff is used in addition to a precordial stethoscope for evaluation of the cardiorespiratory system (Fig. 10). The pulse, respirations, and blood pressure constitute the main criteria for evaluation of the patient's condition during surgery. Either the pulse and respirations or the blood pressure is obtained individually by alternately clamping one arm of the Y-tube and shunting sounds through the long arm of the tube to a molded earpiece in the anesthetist's ear.[5]

Infants exchange about one-half of their body fluid reservoir during a day, as compared with one-seventh in the adult.[6] Infants over 6 months of age also lose a greater volume of water by vaporization because of a higher metabolic rate. This increase in metabolic rate results in a relatively greater minimum urinary volume necessary for urinary excretion of waste products. This rather massive volume of fluid exchange in the normal infant is increased during surgery, and early adequate fluid replacement is therefore important. An infant's daily sodium chloride requirement is about 1 gm. and patients experience salt retention during surgery and immediately

Fig. 9.—Endotracheal tubes, connectors, and laryngoscopes for infants. DeLee mucous trap and plastic catheter for tracheobronchial aspirations.

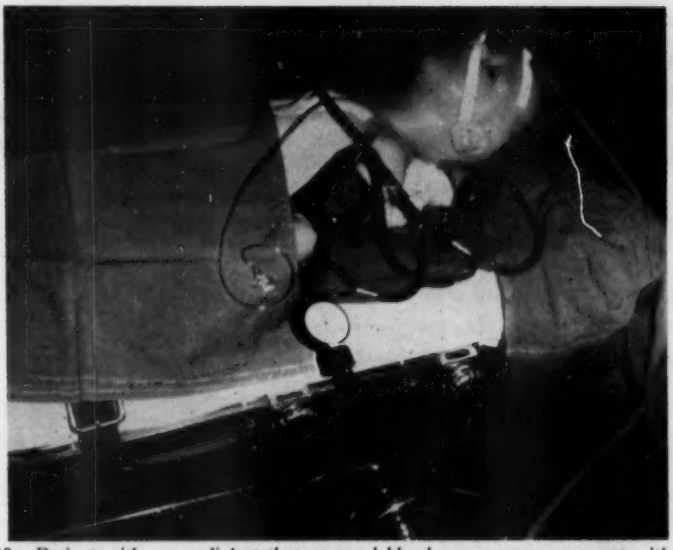

Fig. 10.—Patient with precordial stethoscope and blood pressure arrangement with common earpiece.

Fig. 11.—Phlebotomy with No. 18 polyethylene catheter, three-way stopcock, and syringe for blood administration.

postoperatively. Intravenous 5% dextrose in water is therefore used in most operative cases and is always given to those in whom it is anticipated that their oral intake postoperatively will be inadequate.

When significant bleeding or prolonged surgery is anticipated, a phlebotomy is done in the operating room just prior to surgery. Usually the saphenous vein at the ankle is cannulated with a No. 18 polyethylene catheter to which is attached a three-way stopcock. This enables us to administer blood with a syringe, which is much more accurate than by gravity drip (Fig. 11). The blood

volume of an infant is approximately 100 cc. per kilogram, as compared with 90 cc. per kilogram in the average adult. A patient weighing 5 kg. loses 24% of his blood volume by losing only 120 cc. of blood. A 70 kg. adult must lose 1500 cc. of blood to reduce his blood volume an equal amount. In infants, therefore, it is of importance to replace significant blood loss during surgery, and in many instances this may only be a few cubic centimeters.

Summary

In pediatric anesthesia it is important to eliminate psychic trauma by proper psychologic preparation, proper premedication, and a smooth induction. The anesthetic risk is decreased and good working conditions for the surgeon are provided by means of proper mechanical aids. There are basic differences in fluid volume requirements in infants and adults; hence the importance of correct fluid and blood therapy in pediatric patients.

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Fig. 12.—Postanesthesia recovery room care. Note wall oxygen and suction.

Recovery

It is most desirable to have the pediatric patient able to maintain his own airway upon completion of the operative procedure. The patient is taken to the recovery room adjacent to the surgical suite, where a nurse is in constant attendance until the patient has fully recovered from the anesthetic. Oxygen and suction as well as professional personnel are immediately available for the care of these patients before returning them to the less accurately supervised surgical floors (Fig. 12).

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Pupillary Blockage by a Subluxated Lens, Causing Glaucoma

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Subluxation of one or both lenses in a child presents the ophthalmologist with a problem entailing a difficult decision. Agnew [1] stated in 1885 that cases of subluxation of the lens were embarrassing. They still are. The results of surgical intervention in these cases are by no means uniformly successful. Complications, not only during the operation but in the postoperative period as well, are common and the visual results are often not good. On the other hand, if the lens is allowed to remain where it is, certain serious complications, including glaucoma, may arise.

Vail [2] cautions that the eye should be left alone unless specific indications are present for removal of the lens. Among his indications for surgical intervention he includes glaucoma and says that the lens sometimes comes into the anterior chamber, but, in this article, makes no mention of glaucoma produced by blockage of the pupil by the lens. Most of the literature on subluxation of the lens does not mention this complication, although it is by no means unknown. Duke-Elder [3] states that glaucoma may be produced by the luxated or subluxated lens and indicates that one mechanism is blockage at the pupil. Chandler, in 1947,[4] describes blockage of the pupil by vitreous in a case of subluxation of the lens causing glaucoma, but he does not mention the lens blocking the pupil. However, in a subsequent article in 1951 [5] he gives a brief but very good description of the latter condition. Friedenwald,[8] in 1932, described the case of a child with a dislocated lens floating free in the anterior chamber. For a time it did no harm; then suddenly one day the pupillary margin made contact with the posterior lens capsule, blocking the pupil. Iris bombé and glaucoma developed. By measuring the anterior chamber of the fellow eye, Friedenwald was able to determine the rate of aqueous flow. This case differed from mine in that the lens was completely luxated and lay free in the anterior chamber.

Harshman [6] reports a family in which 10 members had hereditary glaucoma, and 6 of these had dislocated lenses. None of these cases of glaucoma responded to the usual medical or surgical treatment and the only effective therapy was removal of the lens, even though no mention was made of blockage of the pupil by the lens in any of them. The writer describes several mechanisms by which the lens could cause glaucoma, such as (1) displacement of the lens into either the anterior chamber or the vitreous body and (2) contact with or pressure upon the ciliary body, giving rise to irritative vasomotor reaction or to local edema. He does not mention blockage at the pupil.

Lloyd [7] reports a series of 21 cases of Marfan's syndrome observed for from 5 to 14 years and 25 cases observed for a shorter period. He concludes that all cases of luxation or subluxation of the lens in children should be considered as Marfan's syndrome until proved otherwise, and he, like the others, agrees that the results of surgery are discouraging. Here, again, no mention is made of blockage of the pupil.

Report of a Case

The case of a child under my care emphasizes so strikingly blockage at the pupil and the need for emergency operation, as

Received for publication May 7, 1956.

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well as certain other unusual features, that it seems worth reporting.

Little A, age 2½ years, was sent to me on the afternoon of March 22, 1955, by an ophthalmologist who had seen him in the morning and had made a diagnosis of bilateral megalocornea and bilateral subluxation of the lens. Both pupils had been dilated by a mydriatic. No signs of Marfan's syndrome were apparent in either the child or his parents. The patient's corneas measured 12 mm. in diameter. The lens, in the right eye, lay in the anterior chamber; it was globular in shape and smaller than normal. The iris was tremulous. The vitreous hyaloid was ruptured, and vitreous was seen extending through the pupil into the anterior chamber. In the left eye, the iris was tremulous, the lens was dislocated downward so that the upper margin lay across the pupil, and zonular fibers (somewhat stretched out) could be seen extending from the upper portion of the equator. The vitreous hyaloid in this eye appeared to be intact.

Upon making inquiry, I found that the right lens had not been in the anterior chamber at the time the first ophthalmologist examined the eye in the morning. The patient was hospitalized and an attempt made to trap the lens by instilling pilocarpine. The pupil was somewhat smaller the next day, and the lens was raised to more of a central position in the anterior chamber. On the second day, March 24, the pupil was still smaller but the lens was gone. Another attempt was made to trap the lens and atropine and hydroxyamphetamine (Paredrine) were instilled on March 25, and again the lens appeared in the anterior chamber. The patient was sent home with instructions to instill pilocarpine. On March 28 the lens disappeared again. When he appeared for examination, on April 1, it was found lying in the posterior chamber at 6 o'clock. The equator barely came up to the pupillary margin.

We were faced with a decision of removing the lens surgically or leaving the eye alone. Surgical intervention was fraught with the hazards of a technically difficult procedure, probable vitreous loss, and possible late retinal detachment. On the other hand, if nothing was done, there was a likelihood of one or more of another set of serious complications. Since the parents were intelligent and cooperative, it was decided not to intervene for the time being. The symptoms of acute glaucoma were described to them, and they were warned to be alert for these or other signs of complications and were requested to bring the patient for observation at regular intervals. Because the subluxated lens was one of the pupillary area, cataract glasses were prescribed.

When the patient was next seen, on May 2, the right lens was found lying low behind the iris. It did not enter the pupillary area. The glasses had been highly satisfactory, and the parents thought his intellectual development had been accelerated. It was obvious that he was using only the right eye. The subluxated lens in the left eye lay across the pupil and interfered materially with vision.

He was brought in again on June 1 with a story that he had been ill for three days with lack of appetite, vomiting, and redness of the left eye (not the right one, which we had been watching so carefully). Examination revealed that the left pupil had been corked by the lens, which extended part way into the anterior chamber and was squeezed by the sphincter. The iris ballooned forward, the cornea was steamy, and the sclera injected (Fig. 1). The right eye was perfectly quiet.

The patient was hospitalized and pilocarpine used, without improvement. A mydriatic could have been used to better advantage. On June 3 a left lens extraction was done through a corneal incision (sketch, Fig. 2). Four preplaced sutures were used. During the manipulations necessary for placing these sutures, the cornea cleared; i. e., the steaminess disappeared, the eye became noticeably softer, and the lens slid back out of the pupil. One peripheral iridectomy was made in the 12 o'clock meridian. The capsule was grasped by Arruga forceps and the lens extracted by means of

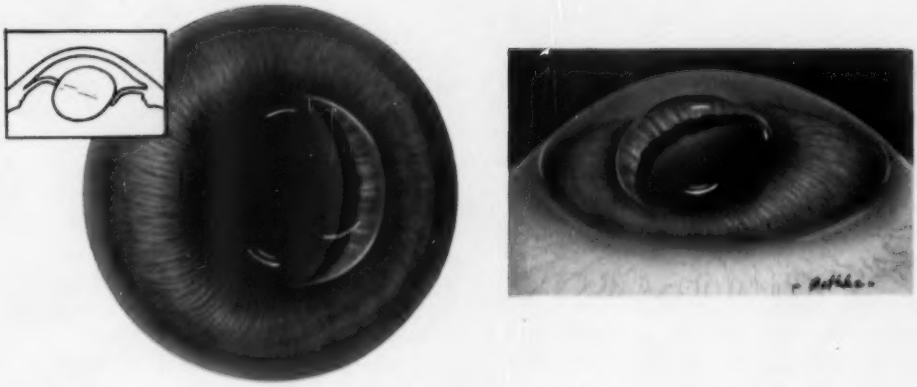

Fig. 1.—Left lens caught in and obstructing the pupil, causing secondary glaucoma.

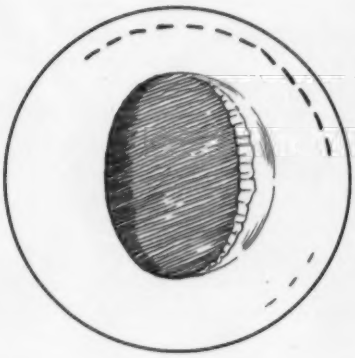

Fig. 2.—Dotted line indicates the position of the corneal incision used for extracting the lens.

Fig. 3.—Appearance of the right eye when examined on Nov. 23. The lens had receded behind the iris, but it must have lain in firm contact with Descemet's membrane for some time in order to produce the edema found there.

combined external pressure and traction. The zonule separated with some difficulty but no vitreous was lost, nor did any other complication arise. The hyaloid apparently remained intact. Recovery was uneventful, and the child left the hospital on June 15.

He returned for observation at intervals throughout the summer and autumn. A cataract lens was prescribed for the left eye also, and, since the subluxated lens in the right eye continued to remain down below the pupillary margin behind the iris, he enjoyed binocular vision. One thread-like adhesion developed between the anterior surface of the iris and the incision in the 1:30 meridian, causing the pupil to be pear-shaped, but not displacing it materially.

The right pupil was dilated again on November 23 to see if the lens would come forward into the anterior chamber. It did not. However, on December 7 the mother reported that the right pupil had remained dilated after the use of the mydriatic on November 23; the child was ill again, would not eat, had been vomiting, and the right eye was red. He was immediately driven 70 miles to my office. Upon inspection, the pupil was found to be small, whereas the mother said it was still large when they left home. The child had been fussy and crying the first part of the trip but had suddenly dropped off to sleep and since that time seemed comfortable. The central 6 or 7 mm. of the cornea presented a cloudy appearance, blurring the pupillary margin. The corneal microscope revealed that this cloudiness was due to edema of the endothelium and folds in Descemet's membrane. The iris appeared normal and tactile tension was normal. The lens was found to be lying at the bottom of the eye behind the iris. Obviously this lens also had been caught part way through the pupil, which it had obstructed and had lain in contact with the posterior surface of the cornea for some time (Fig. 3).

The patient was hospitalized, and on December 12 a right lens extraction was carried out in a manner similar to the one on the left. Again there were no serious surgical complications, but this time the lens could not be grasped with a capsule forceps. Instead, a small loop was slipped behind the lens, and the lens was brought forward against the posterior corneal surface and delivered by sliding it across the cornea as external pressure was made with a hook. No vitreous was lost, although vitreous had been seen lying across the pupillary margin in previous slit-lamp examinations. Recovery was uneventful except that once more an adhesion developed between the anterior surface of the iris and the incision. This adhesion was a little larger than in the left eye and displaced the pupil upward slightly. Nonetheless, the practical result was excellent and, when last seen, on March 27, 1956, both pupils were clear and the tactile tension was within normal limits, although a little higher in the right than the left eye.

Comment.—In this case, glaucoma developed in both eyes purely and simply because of blockage of the pupil by a subluxated lens. Until the lens blocked the pupil, no glaucoma developed. The right lens apparently lay in contact with the ciliary body in the bottom of the eye for a considerable period of time, but there was no evidence of vasomotor reaction or local edema. Nor was there any difficulty when the lens lay free in the anterior chamber. Peripheral iridectomy, such as was done in the left eye, could have been the only operative procedure and would have served to prevent the recurrence of glaucoma from blockage of the pupil by the lens, but the eyes would still have been subject to the other complications commonly occurring. We were unusually fortunate in that the anticipated surgical complications did not materialize, not even loss of vitreous. This had been fully expected, especially in the left eye, where vitreous was seen in the anterior chamber.

The fact that surgery was so highly satisfactory in these two eyes does not mean that the usual difficulties have been overcome. If confronted with another similar situation,

the same dilemma would obtain—should the lens be removed or should it not?

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Unilateral Lid Retraction

Association with Common Carotid Thrombosis

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In 1852 Claude Bernard first described his classical triad of mydriasis, widened palpebral fissure, and slight exophthalmos. Since the original account by Bernard, vasoconstriction, hypothermia, and hyperhidrosis have come to be considered within the same syndrome. Often these latter symptoms are absent, slight, or latent. Pupillary reactions to light and accomodation usually remain, but they may be decreased.

The syndrome is the result of a central or peripheral irritative lesion. Centrally, it can be located in the hypothalamus, midbrain, medulla, or cervical cord and result from neoplasm, encephalitis, or syphilis. Peripheral lesions include cervical rib, aneurysms of thoracic vessels, mediastinal tumors, tuberculous pleurisy, retropharyngeal tumors, swollen thyroid, enlargement of cervical lymph nodes, hematoma in the neck, and aortic dilatation.[1] To our knowledge, a thrombosed common carotid artery has not been associated with lid retraction.

Shapiro reported on 17 cases of spontaneous thrombosis of the carotid arteries.[2] Generalized findings were the following: motor abnormalities (weakness, drowsiness, incontinence, and restlessness); headaches (ipsilateral or generalized); sensory changes (paresthesias, etc.); aphasia (motor and sensory); psychiatric symptoms (depression and euphoria); convulsions; head noises; dizziness, and sneezing. Eye findings were transient blindness, homonymous hemianopsia, and primary optic atrophy. Other symptoms reported in the past have been diplopia, ptosis, miosis or mydriasis, papilledema, and vertical paralysis.[3,4] Widened palpebral fissures, or lid retraction, was not mentioned in any of these patients.

Submitted for publication July 23, 1956.

William Beaumont Army Hospital, El Paso, Texas; Ophthalmology Service (Capt. Elander); Chief, Ophthalmology Service (Capt. Bedrossian); Chief, Neuro-Surgery Service (Major Schaerer).

Report of a Case

A 33-year-old white woman was admitted to the Eye Service of William Beaumont Army Hospital on Oct. 1, 1955, complaining of gradual progressive prominence of her eyes over the past one and one-half years. This had become most noticeable in the right eye during the month prior to admission (Fig. 1). She had also noticed recent dull intermittent right-sided headaches, nervousness, irritability, and forgetfulness. About one month before admission she awoke one morning with double vision that cleared within an hour, without recurrence. Awkwardness while walking at night developed, along with occasional dizziness and clumsiness in picking up objects. There were no symptoms characteristic of hyperthyroidism.

Physical examination was normal except for the eye findings and a positive Hoffmann's sign on the right.

Ophthalmic examination: The uncorrected visual acuity was 20/20 in each eye. Marked prominence of the right eye was present. Conjunctivae, sclerae, extraocular movements, visual fields, and intraocular pressures were normal. Pupils were equal bilaterally and reacted equally in accomodation and to light. Exophthalmometer readings were as follows: right eye, 20; left eye, 18. Fundi were normal except for sheathing of vessels at the nasal edge of the right disc.

Laboratory data: Normal urinalysis, hemogram, serology, protein-bound iodine,

Fig. 1.—Appearance of eyes on admission, showing retraction of right upper lid and equal pupils.

and blood cholesterol. Spinal tap revealed a pressure of 200 mg. of saline, protein of 40 mg. per 100 cc., and sugar of 69 mg. per 100 cc. X-rays of the chest, skull, and orbits were normal.

Course in the hospital: After this initial work-up on the eye service, the patient was transferred to the neurosurgical service, where an arteriogram of the right common carotid artery was performed. A complete obstruction at the level of the third and fourth cervical vertebrae was found (below the bifurcation of the carotid), but there was good posterior cerebral filling from the vertebral artery. After the procedure, a right stellate ganglion block was performed, which resulted in temporary equalization of the palpebral fissures. In January, 1956, the right fissure again responded favorably to a second stellate block. This was followed by a right superior cervical ganglionectomy, which resulted in elimination of the lid retraction. Postoperatively the palpebral fissures are equal. The right pupil is 1 mm. smaller than the left. No change in sweating is present on the right, and there is no dilation of the pupil with 1:1000 epinephrine or cocaine. The generalized symptoms the patient had experienced were also greatly improved, and she is very pleased with her normal appearance (Fig. 2).

Fig. 2. — Appearance after superior cervical ganglionectomy, showing equal palpabral fissures.

Summary

A case of unilateral lid retraction associated with "spontaneous" thrombosis of the common carotid artery is presented.

William Beaumont Army Hospital, Fort Bliss.

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Superior Oblique Tendon Sheath Syndrome

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At the strabismus symposium in Iowa City in 1950, Brown presented a preliminary report on a new syndrome,[1] which he referred to as the superior oblique tendon sheath syndrome. At the more recent symposium, in New Orleans, he amplified his original presentation and stated that the following criteria were necessary for the diagnosis: paralysis of the inferior oblique, little or no overaction of the superior oblique, depression of the eye on adduction, and limitation to passive elevation of the adducted eye. Brown believed that the syndrome was due to a congenitally short sheath of the superior oblique. Whitnall[2] has shown that the sheath is firmly attached to the trochlea. With the eye straight or abducted, the sheath is loose and allows full rotations. However, when the eye is adducted the congenitally short sheath acts as a tight band which prevents elevation.

A patient demonstrating this syndrome was seen in the Motility Clinic of the Illinois Eye and Ear Infirmary, and this case is believed to be worthy of reporting because of the opportunity afforded to reexamine the sheath at a second operation. When the patient was 5 months old, the mother first noted that the child's left eye turned down and in. The deviation was much less when the child tilted her head back, a position which she used much of the time. The child was the product of a full-term normal spontaneous delivery without postnatal complications and had had no illnesses since birth. Examination on June 20, 1952, at the age of 9 months was essentially normal except for ocular motility. Atropine refraction was -0.50 $+4.00$ $\times 90$ degrees in each eye. The child carried her head tilted back about 30 degrees. Fixation in each eye was central and steady. With the head level, the left eye turned down 30 degrees and in 30 degrees. When the child fixed with the left eye in the primary position, there was about 40 degrees of right hypertropia. Versions revealed a paralysis of the left inferior oblique, with overaction of the right superior rectus but no overaction of the left superior oblique. The left eye could not be elevated above the midline in the adducted position, and on dextroversion there was marked depression of the left eye. Looking straight down, the eyes seemed to be straight.

The patient was observed for 18 months without any change in her condition, after which time she was operated on. Under general anesthesia, the left eye could not be moved above the midline in the adducted position, whereas ductions in the other cardinal directions were normal in the left eye and no limitations were found in the right eye. The superior oblique was isolated and its sheath was stripped almost to the trochlea, in a manner similar to the procedure suggested by Brown.[1] The sheath seemed to be about one and one-half times the usual thickness. A great deal of resistance was encountered in bringing the muscle up until the sheath had been cut. After this was done, it became possible to elevate the eye fully. Only the left eye was covered for one day following the procedure. Afterward, an esotropia of about 15 degrees and a left hypotropia of about 20 degrees persisted, and the patient was able to elevate the eye slightly above the midline. On dextroversion the left eye still turned down, and she seemed to have bi-

Received for publication Aug. 29, 1956.

Read before the Chicago Ophthalmological Society, Chicago, April 16, 1956.

From the Motility Clinic of the Illinois Eye and Ear Infirmary of the University of Illinois College of Medicine.

nocular vision looking straight down. One year later, a second operation was performed. Forced ductions showed the same inability to elevate the adducted left eye as before the first operation. The sheath of the superior oblique had completely reformed. Again the sheath was stripped, and it became possible to elevate the adducted eye. In addition, the inferior oblique was advanced at its origin by rolling the muscle over the orbital rim and suturing it to the periosteum, in a procedure similar to that described by Wheeler.[4] Eighteen months after the second operation, with the right eye fixing, there remained about 5 degrees of left esotropia and about 8 degrees of left hypotropia. With the left eye fixing, about 20 degrees of right hypertropia persisted. In the primary position fixation with the right eye was rather constant. The left eye could be elevated about 10 degrees above the midline in the adducted position. Binocular vision was apparently present on looking down, and there was depression of the left eye on dextroversion. The mother stated that, when looking at television, the child tilts her head backwards about 10 degrees.

Comment

The patient's cosmetic appearance has been vastly improved by the two procedures described, although a deviation is still present. I feel reasonably sure that, should we explore the left superior oblique again, we would find that the sheath had re-formed and there would be limitation to elevation in the adducted position by the forced duction test. This result is comparable to those shown by Brown[1] in the postoperative pictures in the Strabismus Ophthalmic Symposium.

Whether the primary pathology in this case is a congenitally short sheath of the superior oblique or a primary paresis of the inferior oblique with secondary hypertrophy of the fascial attachments of its antagonist, as suggested by Urist,[3] cannot be decided. Regardless of the primary etiology, the most successful treatment seems to be an incision or excision of the sheath of the superior oblique combined with a strengthening procedure on the inferior oblique. The case presented demonstrates that stripping of the superior oblique sheath alone is of little value. In all probability, using only a strengthening procedure on the inferior oblique against the resistance of passive rotation up and in would be doomed to failure.

Summary

A case fulfilling all of the diagnostic criteria of a superior oblique tendon sheath syndrome is presented. After the contracted sheath of the superior oblique was stripped, the condition recurred, and a second operation showed that the sheath had re-formed. Combined excision of the sheath of the superior oblique with a strengthening procedure on the inferior oblique at the second operation produced a better result.

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A New Form of Angiodiathermy in Glaucoma with Animal Experiments

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Introduction

In ocular hypertension, the following factors may be concerned: (1) increased resistance to aqueous outflow, (2) increased aqueous formation, and (3) rise of anterior ciliary vessel blood pressure.

Iridectomy, iridosclerectomy, trephination, iridencleisis, goniotomy, and goniopuncture are believed to decrease resistance to aqueous outflow.

While Heine's cyclodialysis was believed by Fuchs and Axenfeld to be one of the angle-opening operations, it was shown by Goldmann and others to be an operation decreasing aqueous formation, as a procedure modifying the neurovascular system in the uvea.[14,15] Therefore, since angle-opening operations are actually most useful, cyclodialysis is comparative rarely applied nowadays in glaucoma.

Though the cyclodiathermy of Weve (1932), Vogt,[19,20] and others is mainly an operation decreasing aqueous production, some one has said that it would be a suitable procedure when other methods of treating glaucoma have failed. After the appearance of cyclodiathermy some further modifications were reported by Wagner,[21] Marr, Linder, Castroviejo, and many others.

Weekers, Forbess, Thomas and Algan, Rama, and others described another modification of retrociliary diathermy as a new technique. Then a cycloelectrolysis was favored by Berens (1945); since then, Weekers and Berens, Sheppard, and Duel[3] also have reported this procedure.

Received for publication March 5, 1956.

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But since 1946 a number of new methods of angiodiathermy and angioelectrolysis have been presented by Albrich,[1] Schreck,[16] Schulte,[17] Kettesy,[9] Biozzi, Arató,[2] Knobloch,[7] and Wolffersdorff.[28] Arató (1952) has described 100 cases of angiodiathermy over five years, and he has confirmed the effect in chronic glaucoma, while no effect could be ascertained in glaucoma with an ocular tension above 40 to 50 mm. Hg.

Kalfus and Kos[8] revealed the topographical anatomical relation between the long posterior ciliary artery and the horizontal rectus muscle in order to progressly perform angiodiathermy.

For the purpose of observing the proper effect of angiodiathermy I have performed some of these operations on various types of glaucoma with an improved method. I have added some experimental studies by means of a ligature and diathermy coagulation of the long posterior ciliary arteries in the rabbit eye.

Angiodiathermy

1. Method

It is advantageous to instill plenty of pilocarpine preoperatively. After cocaine anesthesia, in nervous patients, 0.5 cc. of procaine should be added to epinephrine and then injected retrobulbarly or subconjunctivally.

Instruments necessary: speculum, two forceps, curved scissors, small knife, two squint hooks, two double hooks, two probes, suturing and diathermy apparatus, etc. Also a diathermy brush-like triple electrode must be prepared.

A vertical conjunctival opening about 1 cm. in length must be made as in a tenotomy

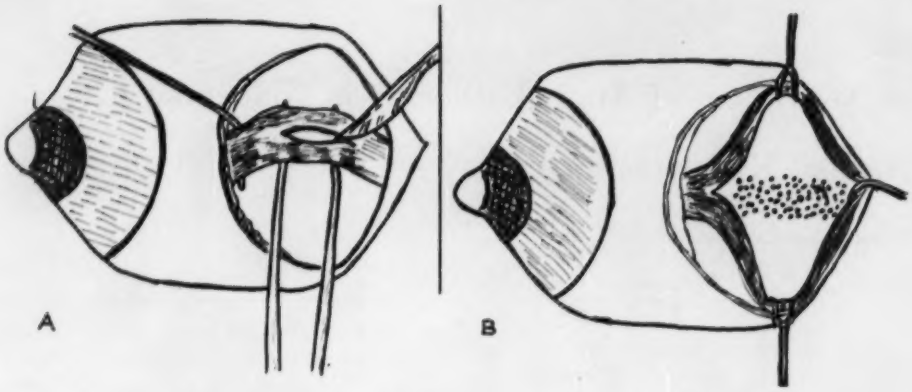

Fig. 1.—*A*, incision of exposed tendon. *B*, after angiodiathermy.

for squint, and the external rectus tendon is exposed with a squint hook. After two tips of an opened forceps are passed under this tendon, a horizontal incision is made in the middle of the tendon with a knife; then the forceps are taken away and the incision of the tendon is drawn apart by two double hooks by an assistant in order to expose the scleral area, which is extended with scissors by the operator (Fig. 1).

After the course of the deep long posterior ciliary artery is estimated locally, the exposed sclera is compressed perpendicularly by a thick probe with adequate pressure for a little while. Just after the pressure is stopped, a pale violet congestive linear sign can be seen as the subscleral course of the artery; then the operator rapidly marks a line on this area by another probe with a solution of a dye, methylrosaniline chloride (Pyoktanin). If this violet sign does not appear, a methylrosaniline chloride line should be painted along about the middle of the tendon course.

Finally diathermy is employed, a series of perforating multiple coagulations being made along this line by means of a triple needle.

After this, the conjunctival wound is closed, and a monocular bandage applied for 24 hours.

The coagulated area should be located from the point of insertion to 14 to 15 mm. horizontally and between 7 and 8 mm. vertically in width. It is intended to produce a small black spot in the process of adequate coagulation by means of a weak electric current. A few spots in the many minimal multiple perforations may show a little prolapse of the vitreous. This is not always harmful. But an exceedingly massive perforation with intense current should be avoided, as it may happen that an insignificant scleral rupture might lead to bulbar phthisis.

2. Course of Operation

Twenty-four hours after the operation, it is necessary to begin drops of 1% pilocarpine five or six times daily for two months and to apply cold compresses for one week, not continuously. The suture should be removed after about one week.

Following a sudden rise of ocular tension right after the operation, a fall of tension usually appears after one to two hours. The lowest tension will be found in the second to fourth day, and a steady state of tension is seen commonly after one to two weeks.

While the favorable effect of this procedure is exhibited in various types of simple glaucoma, less effect is induced in highly elevated tension of chronic glaucoma and in the stage of an acute attack, showing a narrow angle.

Because of fear of bulbar atrophy, I do not use bilateral arterial coagulation in the same eye.

3. Report of Cases

The 32 cases of angiodiathermy are divided into four groups—simple glaucoma, buphthalmos, chronic inflammatory glaucoma, and secondary glaucoma (Tables 1 to 4).

TABLE 1.—*Simple Glaucoma*

Case No.	Age, Yr.	Settled Ocular Tension, Mm. Hg	Observed Month
1	68	15	15
2	50	17	13
3	61	19	13
4	70	20	12
5	58	20	12
6	43	21	12
7	35	22	10
8	75	18	10
9	75	17	9
10	68	19	9
11	33	16	8
12	45	35	8
13	45	18	8
14	28	25	8
15	28	27	7
16	49	20	7
17	50	30	7
18	37	25	6
19	50	24	6
20	63	29	6
21	70	15	6

TABLE 2.—*Buphthalmos*

Case No.	Age, Yr.	Settled Ocular Tension, Mm. Hg	Observed Month
1	2	17	11
2	4	20	10
3	4	19	9

TABLE 3.—*Inflammatory Glaucoma*

Case No.	Age, Yr.	Settled Ocular Tension, Mm. Hg	Observed Month
1	57	30	9
2	57	40	8
3	27	30	8
4	31	25	8
5	30	24	7

TABLE 4.—*Secondary Glaucoma*

Case No.	Age, Yr.	Settled Ocular Tension, Mm. Hg	Observed Month
1	50	30	10
2	45	19	10
3	30	15	8

In the 21 cases of simple glaucoma, 17 eyes showed good results, in all 80%; the treatment was not effective in 4 eyes. In the three cases of buphthalmos all three eyes had the expected results. In the five cases of chronic inflammatory glaucoma, two eyes showed good results and three eyes were unaffected. In secondary glaucoma, two of three eyes had good results and in one eye high tension reappeared.

In the cases in which satisfactory results appeared, a continued drop of ocular tension to normal lasted for as long a time as 6 to 15 months and more.

Sufficient effective results occurred, with almost normal sight and tension, in about 75% of all cases. Half of the other cases of glaucoma, equal to 12.5% of noneffective cases, also had favorable results by a combination with other types of operations, such as iridectomy, iridosclerectomy, and iridencleisis. There were, however, no cases that assumed a malignant course due to angiodiathermy, except some cases that had already reached the stage of absolute glaucoma.

As to postoperative complications, neither cataract with hypotension nor any uveitis was seen following angiodiathermy (Figs. 2 to 4).

4. Animal Experiments

For the purpose of investigation of the nature of effect of the local control of ocular tension and the mechanism of the angiodiathermy, animal experiments were done, using albino rabbit eyes.

(1) *Bulbar Compression Test of Normal Rabbit.*—By means of 50 gm. bulbar compression over a period of 10 minutes with a Bailliart's ophthalmodynamometer, the ocular tension of P_0 (primary tension), P_1 (right after compression ceased), and P_2 (30 minutes after P_1) were measured by Schiötz's tonometer. From these values, the aqueous outflow ratio D was calculated as in the following formula:

$$D\% = \frac{P_0 - P_1}{P_0} \times 100$$

Also, the ratio R (repairing grade of dropped tension, P_1, to the primary level), indicating aqueous formation after compres-

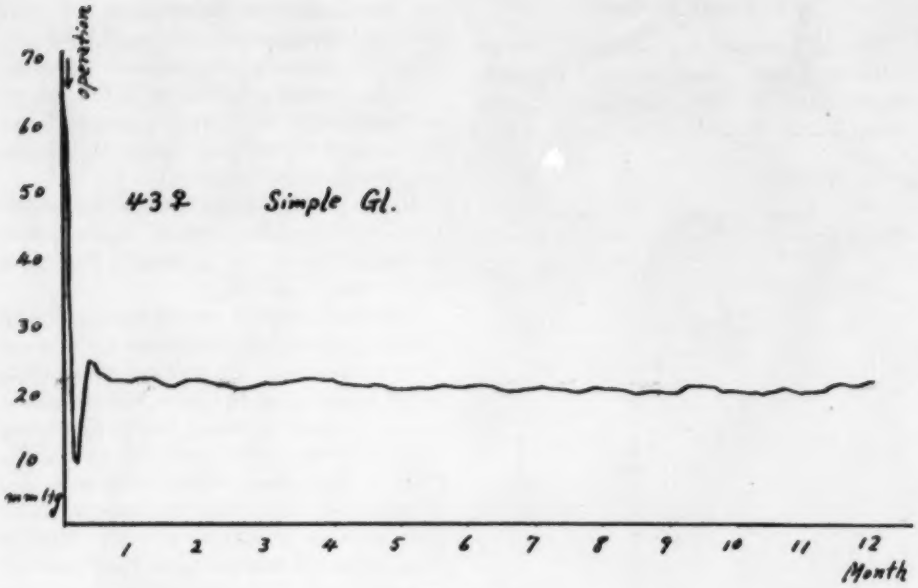

Figure 2

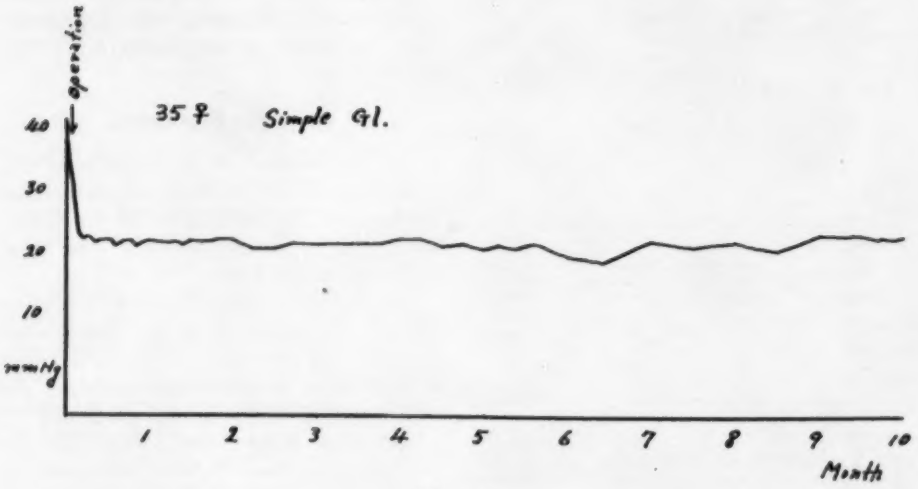

Figure 3

sion ceased, was calculated with the following formula:

$$R\% = \frac{P_0 - P_1}{P_0 - P_2} \times 100$$

And the outflow resistance W was also calculated, with the following formula:

$$W = \frac{31}{P_0 - P_1} - 1$$

(These formulas were previously reported in my monograph, 1954.[18])

Results of the average values of 6 rabbit eyes and the same average values of 30

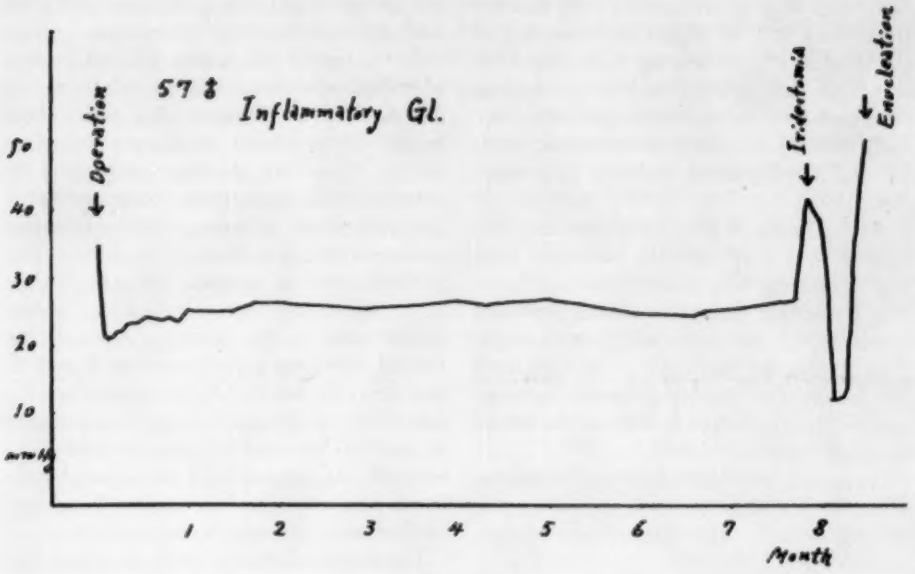

Figure 4

human eyes are shown in Table 5; the nor-

TABLE 5.—*Normal Bulbar Compression Test*

	P_0	P_1	P_2	D,%	R,%	W
Human (30 eyes)	18.6±0.96	7.18±0.56	17.08±0.94	61.3	86.6	1.71
Rabbit (6 eyes)	20.0±0.2	8.0 ±0.3	21.0 ±0.2	60.0	108.0	1.58

mal values of *D* and *W* are almost alike in rabbit and human eyes, but the normal *R* of the rabbit is higher than that of the human eye.

(2) *Bulbar Compression Test of a Rabbit that has Undergone Operation.*—The same animals were divided into two groups—those with angiodiathermy and those with ligature of the long posterior ciliary arteries—and my bulbar compression test and the same tests with various drugs were tested.

Angiodiathermy in rabbits was done in the same way as the above-mentioned operation on the human eye. The operation of ligature of ciliary arteries was done under Percaine local anesthesia. After the conjunctiva was cut, exposing the temporal and nasal scleral surface, both visible long posterior ciliary arteries were stitched with nonabsorbable surgical (silk) suture 1 cm. from the limbus. The wound was closed, and penicillin drops were applied.

Subconjunctival injection of 3% hypertonic saline solution 0.2 cc., 0.1% epinephrine 0.2 cc., 0.5% pilocarpine 0.2 cc., or 0.5% atropine 0.2 cc. was used as a loading test, together with bulbar compression tests 10 to 21 days after operations.

The values of *D*, *R*, and *W* are found in Table 6. According to the effect of angio-

TABLE 6.—*Bulbar Compression Test and Drug Loading Test (Rabbit)*

	Ocular Tension	D, %	R, %	W
Normal bulbar comp. test	20	66	108	1.58
Angiodiathermia test	16	25	150	6.75
Ligature operation test	5	20	900	30.0
with load of saline solution	5	77.7	114	1.21
with epinephrine	16	27.7	0	5.2
with pilocarpine	17	12	−100	9.3
with atropine	28	20	133	4.2

diathermy in a normal rabbit eye, there is an evident fall of ocular tension and an elevation of *W*. Comparing the eyes not operated on, the tendency of whole vessels of the fundus to control with ophthalmoscopically visible areas that have become ischemic, we find a conspicuous decrease in aqueous formation.

Any influence of the epinephrine and pilocarpine injection on the tension after angiodiathermy was nonevident.

It seems that there is a tendency toward imbalance of the autonomic nerves, especially shown by the evident relaxation of the intraocular parasympathetic nervous tone as an after-effect of cutting the arc of the axon reflexes.

Therefore, the calculated high value of *R* and *W* probably would be caused by this dropped tension and constriction of the vessels.

The effect of ligature of the long posterior ciliary arteries in normal rabbit eyes was a definite fall of tension of 5 mm. Hg at 10 days after operation. There was also increase of *W* and vessel constriction. On account of this, the evident parasympathetic relaxation and high values of 900 of *R* and 30 of *W*, an enormous indication, were also considered as the response of low tension and constriction of vessels.

Concerning the drug loading with compression test in the case of the ligature of arteries, interesting results with various drugs were found. Relaxation of the ocular parasympathetic nervous system and decreases of both aqueous outflow and aqueous formation were also evident.

In the test with injected hypertonic saline solution, no significant influence on *D*, *R*, and *W* were noted after ligature, while a distinct elevation of *R* would be estimated in the normal, nonoperated on, eye as control, as in my previous reports, in 1953.[10-12] For this reason, it can be considered that the increased tension caused by the parasympathetic nervous effect, which follows stimulation by saline solution, should have been inhibited by the operation of ligature, registering a decrease of *R* even with the evidently lowered tension.

In the test of pilocarpine injected 21 days after the operation, decrease of *D* and *R* and increase of *W* were also noted, these results being similar to those with epinephrine. This fact, therefore, exhibiting no reaction with pilocarpine, relates evidently the existence of parasympathetic relaxation caused by the operation.

In the test of atropine injected 21 days after operation, there showed up almost similar data in the normal eye as in the control rabbit, such as increase of *R* and *W* and decrease of *D*. As a consequence of that, however, the intraocular blood pressure in the eye operated on was markedly decreased; the existence of imbalance of the autonomic nerve and decrease of aqueous outflow and formation were resumed.

From these facts, it can be assumed that a large role of the effects of angiodiathermy and ligature of arteries is to play on the uveal ciliary nerve plexus as a fluctuating and regulating tendency against the pathological function of the autonomic nervous system, which is closely related to the development of glaucoma.

Comment

The exact mechanism of angiodiathermy inducing a favorable result upon glaucoma is not yet clarified. However, it can be presumed that suppression of aqueous production constitutes the chief favorable effect.

Weekers [26,27] and Weekers and Prijot [24] have presumed that the decreasing resistance of aqueous outflow and opening of the aqueous outlets can be achieved in filtering operations, as in iridencleisis, by means of measuring the resistance of the outflow and episcleral venous pressure.[22,27]

However, with this measuring of outflow resistance after retrociliary diathermy, they have found also the fall of tension and lowering of venous pressure, while the fact of no change of resistance of outflow was presented after this operation. Regarding these facts, they have concluded that the

effect of retrociliary diathermy rests mainly on a decrease of aqueous formation, not concerned with any aqueous outlet, just as in the case of cyclodialysis. They have suggested, therefore, that retrociliary diathermy acts in the same manner as cyclodialysis, and they recommend the combination of other types of operation.

In my data in animal experiments, it was found that the results of angiodiathermy and ligature of ciliary arteries were most in accord with the findings of Weekers and others.

When the operation was performed on a normal rabbit eye, an apparent fall of ocular tension and contraction of whole intraocular vessels (especially in retina and uveal arteries) were visible. Then a reliable decrease of blood pressure of retinal and uveal arterial and venous vessels could be found. A remarkable imbalance of the autonomic nervous system was evident.

After operation on a human glaucomatous eye, a continual fall of tension, as well as recovering of decreased outflow rate to the normal level by my test was indicated. (See previous data of CV, VV % as aqueous outflow rates of our reports in 1953.[12])

It can be concluded that the effect of angiodiathermy on abnormal aqueous hyperformation and the lowering of the abnormal resistance to aqueous outflow is probably due to an inhibitory action, caused by neurovascular changes.

Regarding the reports of some other workers, for instance, Elwyn,[4] Schmerl and Steinberg,[18] and others, it is generally considered to be true that the normal ocular tension increases by the elevating factor produced in parasympathetic excitement and decreases by the falling factor produced in sympathetic excitement.

Concerning the permeability of uveal capillaries, angiodiathermy acts as a suppressor upon this ocular-tension-elevating factor.

Further, it can be assumed that angiodiathermy may cause an evident effect of a neurovascular modulating action, affecting the self-controlling ability of the cycle between uvea and the midbrain center in the human eye.

It was thought that this fact might be supported by my animal experiments of ligature of uveal arteries, because of the tendency toward temporary anoxia and the functional response of the arterial and neurovascular system in the anterior uvea, not of atrophic change in the ciliary body, after the operation. Even in the state of local trigeminal stimulation after the injection of saline solution, the ocular-tension-elevating reaction does not show in the eye operated on. Therefore, the trigeminal reflex in the tension-elevating mechanism, as touched on by Duke-Elder, Courtis and Nunez, Greeves and Perkins,[6] Yokoyama,[20] Gaza,[5] Bailliart-Magitot, and others, is considered of great importance.

As with the human operations, the same facts must be considered with drug loadings in animals in my experiments displaying a neurovascular modulating reaction.

Angiodiathermy can be recommended not only in simple glaucoma but in cases of buphthalmos and hemorrhagic, inflammatory, and secondary glaucoma as well.

In some cases, after long-term observation, there were fewer instances of reappearing high tension after one year, with lowering visual acuity after six months. But those cases which showed an obstruction of the angle have secured comparatively satisfactory results with another kind of operation, such as iridectomy, iridosclerectomy, or iridencleisis.

The visual prognosis coincided with the results of other operations, showing unfavorable results in old cases. I would emphasize the utility of angiodiathermy in the earlier stages of various forms of glaucoma. The need for combinations of other operations with angiodiathermy is strongly indicated in old cases and where there is probable closure of the angle.

Summary

My newly designed angiodiathermy is usable in any case of glaucoma, showing a favorable result with a fall of tension.

Eighty per cent of cases of simple glaucoma register good results, while old glaucomas of angle closure type should be treated by a combination of other procedures.

This kind of angiodiathermy is simple and without side-effects. It is even possible on ambulatory patients.

The effect of angiodiathermy is probably due to parasympathetic imbalance, that is, mainly an inhibiting action on the abnormal aqueous formation.

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A New Slit-Lamp Color Camera

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Although color photographs of good quality have been possible through the conventional slit-lamp microscope with the use of exposures of from a half to one second, it is essential to improve on these speeds if any condition is to be photographed without showing the blur that invariably accompanies slight iris movements, lacrimal flow after blinking, and the movement of the conjunctiva across the sclera that sometimes takes place with concentrated fixation effort.

The reduction of shutter speeds to 1/20 or 1/30 second requires either increased film emulsion speed, greater illumination, or lens systems with a greater light transmission. I have tried all three, and the results of the trials showed that faster film emulsions produce less accurate color reproduction at present, while increase of illumination has to be disproportionate in order to produce an increase of shutter speed. Indeed there is probably a limit to how much light can be forced through a given slit and how much light (and heat) can be tolerated by the average patient.

Some improvement in illumination is possible, and certainly a great reduction in the heat of the illuminant, by using the xenon gas lamp described and used in retinal cameras.[1,2] By changing the condenser lens system of a Haag-Streit slit-lamp, one of these lamps has been fitted to the instrument so that the image of the arc falls into the plane of the slit.

This lamp provides a cool and adequate illumination on about 15 v., 10 amp., which can be used for focusing. Tripping the camera shutter punches 300 amperes through the lamp for a controlled period from $\frac{1}{12}$ second to $\frac{1}{120}$ second, producing an intense flash for that period.

Such a flash has proved to be an improvement on conventional slit-lamp photography, but it still is insufficient for all purposes. The last device to be improved, therefore, is the lens system of the microscope. The conventional slit-lamp microscope has an objective lens, a double ocular, and up to three prisms in the path of each beam. All these absorb much of the available light, and they can be reduced in number with a change of design.

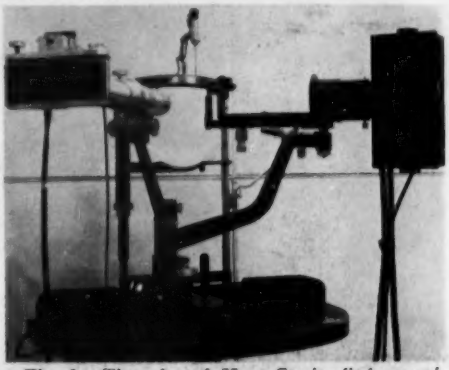

Fig. 1.—The adapted Haag-Streit slit-lamp microscope, showing the new lamp housing. The camera is mounted on the binocular head arm. The knurled knob on the camera tube holds the two sections of tube together.

Two changes were made in the lens system in order to obtain the photographs shown. First, a lens was procured with a large variable aperture; in this case F1-5 maximum. Then the camera body, with a lens-viewed reflex screen and a 35 mm. film holder, was attached to this in such a manner that the length of tube from the lens to the film could be changed.

The reason for this provision is that any variation in the back focal length, i. e., the tube length, produces a relative variation in

Received for publication July 26, 1956.

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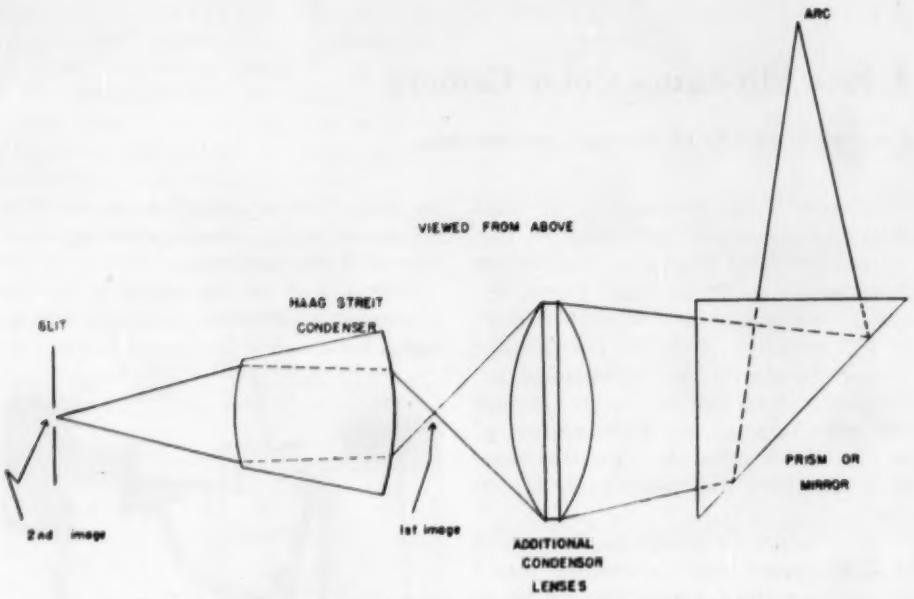


Fig. 2.—Diagram of the condenser lens system produced for the slit lamp.

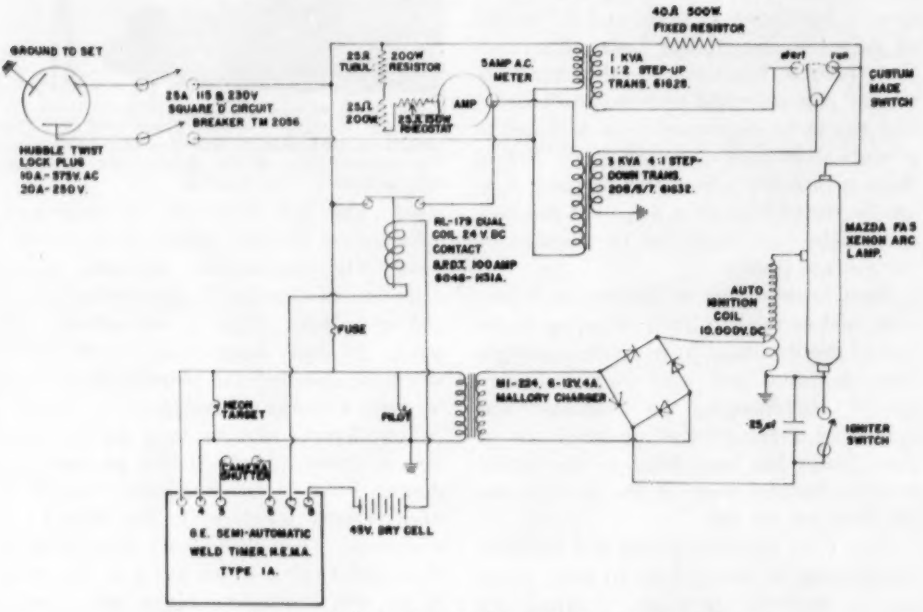
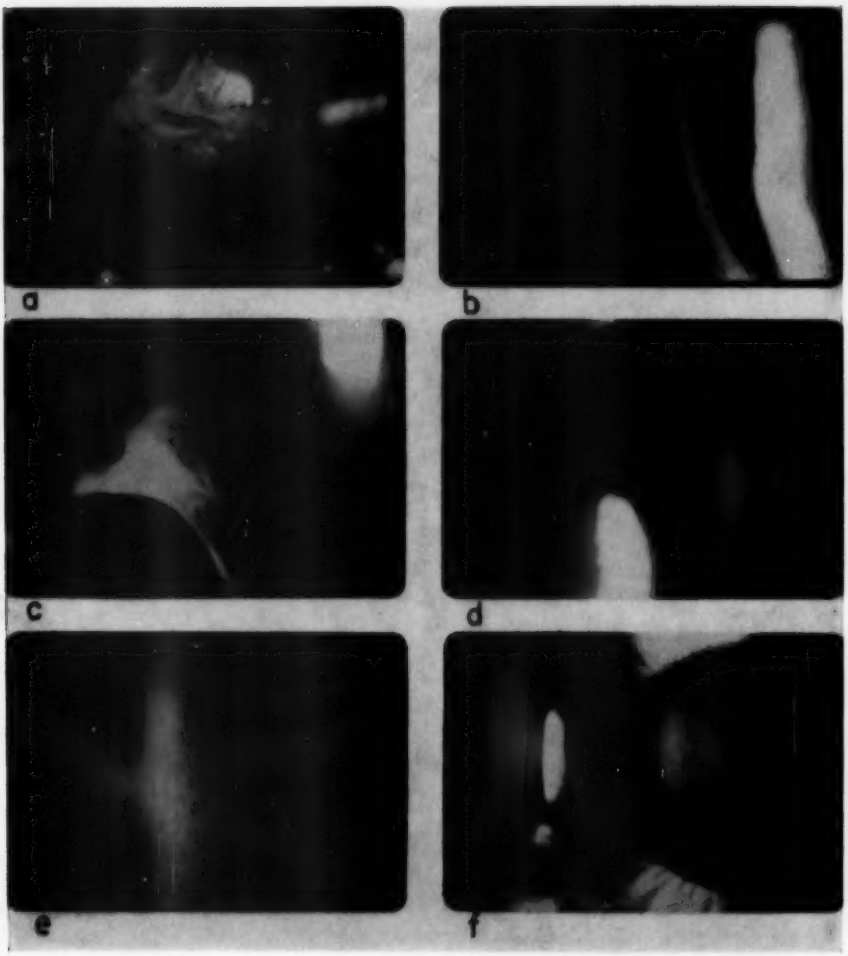


Fig. 3.—The electrical circuit devised to pulse the xenon arc lamp.

image magnification, and to some extent this eliminates the necessity for having different lenses, which with such a large aperture are expensive.

Although the instrument illustrated here is adapted wholly to photography, it is a simple matter to build a camera which can slide into position when the standard bin-



(a.) A corneal lesion photographed at a speed of one second with conventional slit-lamp lighting, and through the binocular eyepiece; subject under light general anesthesia.

(b,c,d,e,f.) Photographs taken at high speed with the equipment shown in Figure 1.

(b.) Argyrosis. The deposition of silver in Descemet's membrane with Hassell-Henle bodies.

(c.) Persistent pupillary membrane, ×30 diameters.

(d.) Normal subject showing both corneal and lenticular reflections from the slit beam, and demonstrating the distance of the anterior surface of the lens behind the plane of the iris.

(e.) The shagreen effect on the surface of a normal crystalline lens; ×30 diameters.

(f.) Photograph of a normal crystalline lens showing the sutures in two directions; ×5 diameters.

ocular microscope head is removed. The problem of passing the slit-lamp past the camera is overcome by detaching the camera and tube from the lens holder and replacing this after the slit-lamp position has been changed to the other side. It would be possible to hinge this, of course, but in the instrument illustrated the simple union performs two functions, exchanging the camera and slit-lamp positions and changing the tube length.

There is little doubt that almost any standard slit-lamp microscope could be adapted in the manner shown for the Haag-Streit and that, with a suitable lens, some photographs could be produced in color with standard illumination.

The building of this camera was made possible by a grant from The Ohio State University Development Fund.

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Anti-Toxoplasma Precipitins in Aqueous Humor

New Application of the Agar-Diffusion Technique

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The Toxoplasma dye test of Sabin and Feldman,[1] which is the mainstay of the present diagnostic regimen in presumptive ocular toxoplasmosis, appears to be inadequate on a number of accounts. Although Woods,* has recently shown that a serum titer of 1:64 is statistically significant in a group of adult patients with granulomatous uveitis, there is no definite proof that a given lesion in the uveal tract of such a patient is due to toxoplasmosis, as opposed to one of the other common granulomatous infections. The simultaneous existence of a positive serum dye test titer, due, perhaps, to a previous systemic infection with Toxoplasma, and a granulomatous uveitis due, for example, to tuberculosis, is a real possibility. Woods, moreover, stated that 25% of a nonuveitis control group which was studied serologically at the Johns Hopkins Hospital also showed positive dye tests at a titer of 1:64. Pursuant to a study of more specific methods for the etiologic diagnosis of ocular toxoplasmosis, a search was made in the present work for precipitating antibodies to Toxoplasma gondii.

Materials and Methods

I. Preliminary Experiments

A. Tube-Dilution Method.—In an early pilot study, rabbit antiserum,† having a Toxoplasma dye test titer of 1:50,000 or more, was tested for the presence of precipitins by means of the standard serial tube-dilution method. Antigen solutions were prepared from the peritoneal exudate of albino mice which had been infected three days previously by the intraperitoneal injection of a standard inoculum of RH strain T. gondii (10^6 to 10^8 organisms per 0.1 cc. of inoculum). The peritoneal exudate was harvested from the infected mice, pooled, and then diluted with an approximately equal volume of 0.85% sodium chloride solution. After the cellular material had been sedimented by centrifugation, the supernatant fluid was drawn off and stored, frozen, in small sterile tubes.

Twofold dilutions of immune rabbit serum, which had been heated previously for one hour at 56 C, were pipetted, in volumes of 0.5 cc., into a series of 10

Received for publication June 7, 1956.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

* Woods, A. C.: Further Studies on the Role of Toxoplasmosis in the Etiology of Endogenous Uveitis, read before the Fifteenth Clinical Meeting of the Wilmer Residents Association, Baltimore, Md., April 19, 1956.

† Specimens of rabbit antiserum as well as mouse peritoneal exudate were supplied by Dr. Leon Jacobs, Tropical Disease Laboratory, National Institute of Allergic and Infectious Diseases, Bethesda, Md., under whose direction the confirmatory Toxoplasma Dye Tests used in this study were also performed.

tubes. The diluent was sterile 0.85% sodium chloride solution. Into these tubes 0.25 cc. volumes of freshly thawed antigen were pipetted. The tubes were shaken well, incubated at 37 C for one hour, and then placed in the refrigerator overnight. Within 24 to 48 hours small amounts of precipitate could be detected in the bottoms of the tubes in titers as high as 1:16. No precipitation was produced when a control antigen containing noninfected mouse tissue protein (spleen) was used.

B. Fractionation of Antiserum.—In the second part of this study human and rabbit antisera of known high dye test titers (1:50,000 to 1:261,504) were fractionated by means of the electroconvection apparatus of Raymond.[2] With the use of phosphate buffer at pH 7.5, at an ionic strength of 0.1, γ-globulin fractions of high purity were prepared by electrophoretic separation. Homogeneous protein solutions containing 0.62 mg. N per milliliter, with Toxoplasma dye test titer of 1:1024, were then tested against the antigen solutions.

C. Gel-Diffusion Method.—The agar-diffusion method of Ouchterlony,[3] as modified by Halbert,[4] was used for testing of γ-globulin fractions. Here, 2.0 gm. of Difco Bacto agar was dissolved in 250 cc. of boiling 0.85% sodium chloride solution. To the molten agar 2.06 gm. of barbital sodium and 1.0 gm. of aminoacetic acid were added. The mixture was well stirred, allowed to cool to 40 C, and then rapidly neutralized with concentrated hydrochloric acid until a final pH of 7.4 was reached. Twenty-five cubic centimeter volumes of warm agar solution were then poured into separate sterile Petri dishes of 10.0 cm. diameter, and allowed to harden at room temperature. The plates were afterward stored in the refrigerator at 7 C. For the absorption of excess moisture, a sterile blotter disc was inserted into the lid of each Petri dish. Six circular reservoirs, each 5 mm. in diameter, were cut out of the agar with a sterile cork borer. An iris spatula was used to lift out the small agar plugs. Arranged in a hexagonal pattern around a larger central well, the peripheral reservoirs were placed at a radial distance of 1.3 cm. from the center. Toxoplasma antigen solution was pipetted into the central reservoir, filling it up to the surface of the agar. Gamma-globulin fractions in various degrees of dilution were put into the peripheral wells. After 24 to 48 hours of diffusion through the agar at 7 C, lines of precipitation could be seen between the antigen well and the corresponding antibody reservoir. The lines were geometrically straight and were always at right angles to an imaginary line drawn between the center of the antigen well and the center of the corresponding antibody reservoir. In Figure 1 a precipitin line is seen only at Well No. 1, where the γ-globulin solution was used in undiluted form. Serial tenfold dilutions (Positions 2, 3, 4, and 5) produced no precipitation. Figure 2 shows another preparation, in which serial twofold dilutions of the antibody were put into the peripheral wells, beginning with undiluted antibody at Position 1. An end-point was reached here at Position 3, where the titer was 1:4. When, as in Figure 3, the identical antibody solution was put into all the peripheral wells, a perfect hexagonal ring of precipitate was formed in the agar, except at Position C, which was filled with a control sodium chloride solution.

II. Experiments with Aqueous Humor

The same technique as described above was modified for the testing of aqueous humor, obtained by paracentesis from patients with presumed toxoplasmic uveitis. Samples of undiluted aqueous (0.15 to 0.2 cc.) were pipetted into the central reservoirs of the agar plates. Into the peripheral wells various antigens of possible

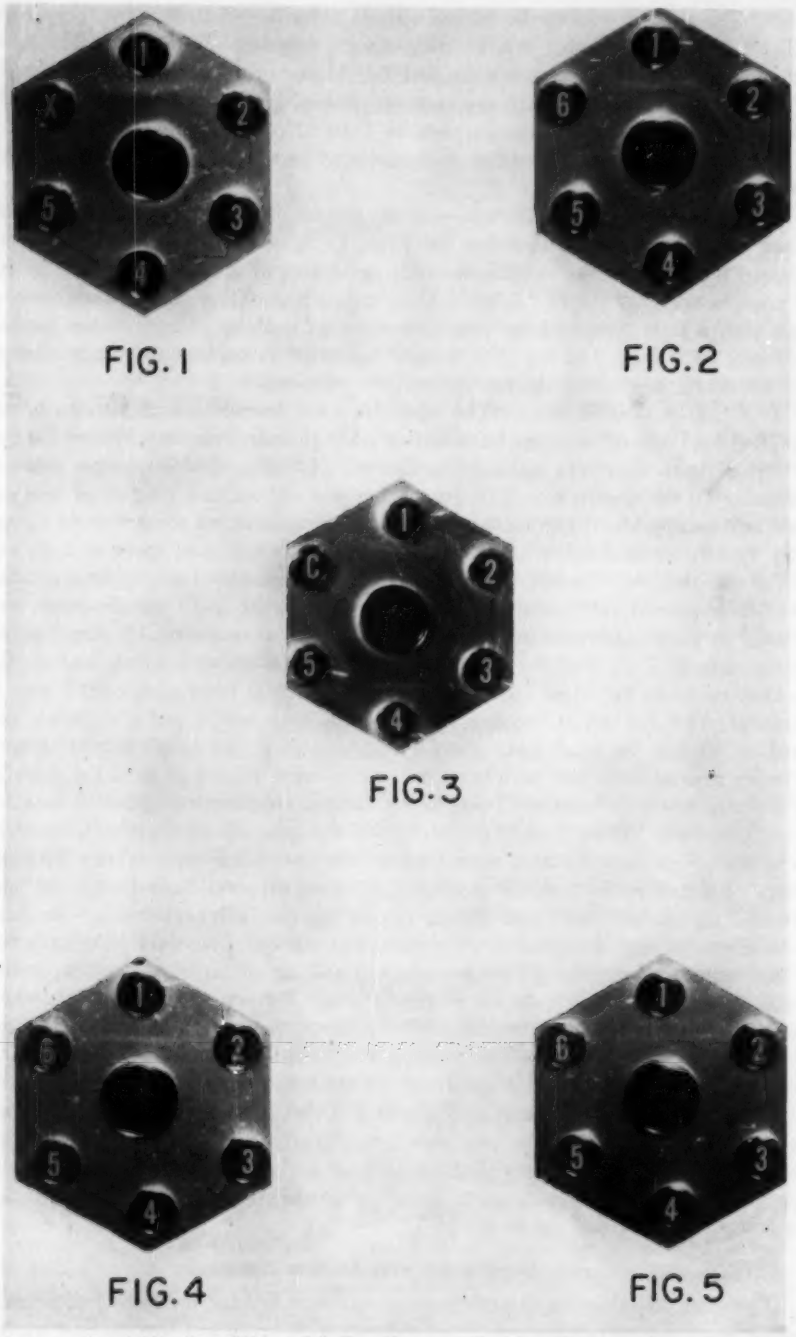

Fig. 1.—Precipitins in rabbit γ-globulin. Center well: Toxoplasma antigen. *1*, undiluted γ-globulin; *2*, 1:10 γ-globulin; *3*, 1:100 γ-globulin; *4*, 1:1000 γ-globulin; *5*, 1:10,000 γ-globulin; *x*, saline control.

(*See legend on opposite page*)

significance in the etiology of the eye disease were pipetted, including antigens from Staphylococcus, β-hemolytic Streptococcus, Histoplasma, and purified protein derivative of tubercle bacilli (Fig. 4).

In every case Toxoplasma antigen was put into Position 1 (Fig. 4), and on every plate a control antigen of normal mouse tissue protein was put into well No. 2. After the wells were filled, the agar plates were stored at 7 C in the refrigerator and observed daily thereafter.

Results

1. *Serum.*—Lines of precipitation from the reaction of serum antibody with Toxoplasma antigen were observed in agar after 24 to 48 hours in the cold. The maximum dilutions of sera at which precipitin lines could barely be perceived ranged between 1:4 and 1:8. Gamma-globulin fractions prepared from these same sera yielded identical lines of precipitation in agar when they were tested with the antigen. The maximum dilution at which the γ-globulin preparations yielded a barely preceptible precipitin line was 1:32.

2. *Aqueous Humor.*—In 4 samples of aqueous humor out of a total of 15 tested, precipitin lines were observed in the agar at Position 1. In two of the specimens, precipitation was observed after 48 hours. Precipitin lines in the other two specimens became perceptible only after three and four weeks, respectively. Of the 15 cases tested, 11 were strongly suspected of having toxoplasmic uveitis on the basis of high dye test titers, positive skin tests, and compatible fundus lesions. Two of the four patients with positive tests had moderately severe anterior uveitis, with cells and flare in the anterior chamber, as well as active chorioretinal lesions at the posterior pole. In some instances sufficient aqueous humor was obtained to perform a simultaneous Toxoplasma dye test on the same material. The results, insofar as they are now available, are presented in the Table.

Comment

At present, it can only be stated that precipitating antibodies to T. gondii have been found in the eye. If γ-globulin assays performed simultaneously on the aqueous humor and serum should subsequently show that there is relatively more antibody in the anterior chamber than could be accounted for on the basis of permeation of the blood-aqueous barrier alone, it could be concluded that there was local formation of antibody in the eye. This method of testing would therefore prove useful in establishing the presence of specific Toxoplasma infections of the uveal tract.

In his studies on experimental leptospiral uveitis, Witmer [5] has inferred that there is local intraocular formation of antibody. There is some evidence to suggest

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Fig. 2.—Precipitins in human γ-globulin. Center well: Toxoplasma antigen. *1,* undiluted globulin; *2,* 1:2 γ-globulin; *3,* 1:4 γ-globulin; *4,* 1:8; *5,* 1:16; *6,* 1:32.

Fig. 3.—Identical precipitins, rabbit γ-globulin. Wells *1* to *5*: undiluted γ-globulin. Center well: Toxoplasma antigen. Well *c*: saline control. Note joining of the individual precipitin lines.

Fig. 4.—Aqueous humor from uveitis patient (Case 2). Center well: aqueous humor, undiluted. *1,* Toxoplasma antigen; *2,* mouse tissue control antigen; *3,* staphylococcal antigen; *4,* steptococcal antigen; *5,* Histoplasma antigen; *6,* purified protein derivative of tubercle bacilli No. 2 (Sharp and Dohme).

Fig. 5.—Aqueous humor from uveitis patient (Case 3). Center well: aqueous humor, undiluted. *1,* toxoplasma antigen; *2,* mouse tissue control antigen; *3,* staphylococcal antigen; *4,* streptococcal antigen; *5,* Histoplasma antigen; *6,* PPD No. 2.

Comparison of Dye Test Titers in Serum and Aqueous Humor and Development of Precipitin Lines in Agar

Case	Serum Dye Test	Aqueous Dye Test	Precipitin Line
1	1:65,276	1:16	+
2	1:261,504	1:32	+
3	1:1024	----	+
4	1:1024	----	+
5	1:256	1:16	Neg.
6	1:1024	Neg. at 1:4	--
7	1:1024	Neg. at 1:4	Neg.
8	1:1024	1:16	Neg.
9	1:1024	Neg. at 1:4	Neg.
10	1:256	Neg. at 1:4	Neg.
11	1:261,504	----	Neg.
12	Neg.	Neg.	--
13	----	----	Neg.
14	----	----	Neg.
15	1:256	Neg. at 1:4	Neg.

that this may also be the case in toxoplasmic uveitis. For example, there is a discrepancy between the dye test titers of aqueous specimens which give precipitin lines and the highest dilution of the corresponding blood serum or γ-globulin preparation which will give barely perceptible precipitin lines. The dye test titer on the aqueous specimen in Case 2 was 1:32, for example, whereas the dye test titer on the final dilution of his serum which gave a barely perceptible precipitin line was 1:256. This indicates a disproportionality between the relative amounts of precipitating antibody and dye test antibody in the two fluids. To explain this, it might be supposed that the precipitating antibody and dye test antibody are two distinctly different substances, and that there is relatively more of the precipitin elaborated in the eye in this case. The presence of "blocking" antibody in the serum and γ-globulin fractions could also explain this discrepancy. From the data currently available we cannot conclude that the detection of anti-Toxoplasma precipitins in the aqueous is more sensitive or more specific than the Toxoplasma dye test performed on the same material.

The method of agar diffusion as presented here has a more general interest as well; it offers the possibility of testing the same small quantity of aqueous humor against multiple antigens simultaneously. As such, it promises to be a valuable tool in assessing the etiology of various types of uveitis the diagnosis of which has heretofore been vague and speculative.

Summary

A heat-stable precipitating antibody to Toxoplasma gondii has been obtained from the anterior chamber of the eyes of four patients with presumptive toxoplasmic uveitis. Detection of the antibody was made through the use of an agar-diffusion technique.

This antibody appears to be identical with a precipitin obtained in purified γ-globulin fractions of serum from patients with high Toxoplasma dye test titers.

The possibility that the Toxoplasma dye test antibody and the precipitating antibody are two different entities is discussed.

Drs. Leon Jacobs, Bethesda, Md.; Seymour Halbert, New York, and David Donaldson, Boston, all made significant contributions to the work here presented.

National Institutes of Health.

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Escherichia Coli Panophthalmitis from Pyelonephritis

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Report of a Case

A 54-year-old Puerto Rican man first entered Mount Sinai Hospital, on May 2, 1956, with a complaint of swelling, pain, and sudden blindness of the left eye of approximately five days' duration.

Five days prior to his admission the patient awoke to find his left eye very painful and swollen and without vision. Prior to this episode the vision in this eye had been good. The patient had used eyedrops from his drugstore for his eye condition and on the day of admission was given an injection of penicillin by his local physician, who referred him to the hospital.

The past medical history revealed nocturia, difficulty initiating his stream, and a thinning of the stream for the previous five months. In addition, a diagnosis of diabetes had been made four years previously, which required no insulin until approximately two months prior to admission. At the time of admission, the patient was on 50 units of isophane (NPH) insulin daily. The blood sugar two weeks prior to his admission was over 400 mg. The remainder of the past history was essentially negative.

Examination of the eyes revealed the following findings: Right eye: The pupil was round and reacted well to light. The extraocular movements were intact. There were some early cortical lenticular opacities. The disc was of good color and delineation, while the vessels appeared to rise normally and were of good caliber. The arterioles showed an increased light reflex, and there was slight arteriovenous compression. In the perimacular region there were a few hard yellowish waxy exudates with small punctate hemorrhages scattered over the posterior pole. The intraocular tension was 20 (Schiøtz). Left eye: There was marked edema and erythema of the lids. There was an intense chemosis of the conjunctiva, so much so that the upper bulbar conjunctiva hung down as a fold over the cornea. There was a moderate amount of injection of the ciliary and bulbar conjunctival vessels. The cornea, however, was clear. The anterior chamber was completely obliterated, with the iris pressed against the posterior surface of the cornea. The iris was clear. The pupil was in the mid position. There was a complete lenticular opacity, and no fundus details could be seen. The eye was stony hard to palpation. Visual acuity in the right eye was normal, while in the left there was no light perception. It was felt that this was an acute glaucoma, but whether it was primary or secondary could not be immediately ascertained.

The patient was given a retrobulbar injection of 2% procaine (Novocain) hydrochloride with epinephrine, 500 mg. of acetazoleamide (Diamox) intravenously, and drops of pilocarpine nitrate 2% and physostigmine (Eserine) salicylate 0.25% every 10 minutes. Despite the antiglaucoma therapy, the tension in the left eye still remained elevated 24 hours after admission, measuring 80 (Schiøtz). The cornea and iris remained clear, while the erythema of the lids and chemosis of the conjunctiva were unchanged. It was thought at this time that we might be dealing with an endophthalmitis.

On the evening following admission the patient had a temperature of 104 F. Specimens for blood and urine cultures were taken at that time. The patient's chest was clear to percussion and auscultation. The urine was cloudy and loaded with white blood cells; there was a trace of albumin

Received for publication July 6, 1956.
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and 4+ sugar. Gram stain showed many large Gram-negative bacteria. The patient, because of his urinary symptoms, was started on sulfisoxazole U. S. P. (Gantrisin) and tetracycline U. S. P. (Achromycin).

On the second hospital day, while on tetracycline and sulfisoxazole, his temperature fell to 99 F. Catheterized urine showed a residual of 1200 cc., and a Foley catheter was left in place. The original blood culture was reported as positive for Escherichia (Bacillus) coli in all flasks and was sent for sensitivity studies, which showed it to be most sensitive to nitrofurantoin (Furadantin) and approximately four times as resistant to tetracycline. All other antibiotics were of no consequence. Urine cultures revealed the organism to be E. coli, once again very resistant to all medication but nitrofurantoin and tetracycline, to both of which it was sensitive.

On the third hospital day the edema of the lids had somewhat receded but the chemosis of the conjunctiva remained. However, the anterior chamber was no longer clear, and there was a dark murky color to the iris. The tension was 60 (Schiøtz), whereas on admission it had been over 80. On the fourth day a small hypopyon was present and, at the corneoscleral junction temporally, a small collection of pus was noted subconjunctivally. Three days later there was a spontaneous perforation of the globe at the temporal limbal area. A large amount of pus was obtained, which was sent for culture and sensitivity determinations. Gram stain revealed many Gram-negative organisms, while culture revealed E. coli of the same sensitivity as that recovered from the urine and the blood. The eye continued to drain copious amounts of purulent material. The patient's temperature fell to normal levels with the perforation. The patient had diagnostic intravenous pyelograms and retrograde pyelograms performed and was cystoscoped, with a final diagnosis of a left pyelonephritic kidney without organic obstruction, for which a nephrectomy was performed. The kidney was found to have multiple cortical abscesses and papillary necrosis and was pyelonephritic, with a peripelvic abscess.

Comment

The etiology of endophthalmitis has been classified into three main groupings by Duke-Elder,[1] and these may be listed as follows:

(1) An exogenous cause whereby, through the introduction of organisms or poisons through a perforating wound or the perforation of a corneal or scleral ulcer, an exogenous type of inflammation is set up.

(2) Secondary infection. Here the original infection is in the uveal tract and the infection is spread by continuity.

(3) Endogenous. The eye is infected from a primary focus elsewhere in the body, through the blood stream.

Of the three, the latter is the one which we shall discuss, as it pertains to the case presented here.

It has been shown that the majority of inflammations affecting the uveal tract, first as an endophthalmitis and later as a panophthalmitis, are caused by the entrance of organisms into the eye via the blood stream from a source elsewhere in the body. That the uveitis can be caused by the actual entrance of micro-organisms into the eye and their lodgement therein has been abundantly proved both experimentally and clinically. This was first established by the classical experiments of Cohnheim (1867),[2] who injected guinea pigs with tuberculous material and at autopsy found the tubercles in the uveal tract, a finding which has been amply confirmed by many others who injected tubercle bacilli into the blood stream. In the same manner, streptococci, pneumococci, and other organisms have been found when injected into animals to produce uveitis, and from the affected eyes the organisms have been recognized by microscopic demonstrations in sections and recovered in culture.

The organisms responsible for these conditions include all which give rise to

pyemic manifestations. In the majority of cases in the literature, bacteriological examinations are lacking. Thus, in Seguini's (1923)[3] compilation of 342 cases, 259 were of undetermined bacterial origin. The commonest organism is the Streptococcus, while the others, not necessarily in the order of their importance, are tubercle bacilli, pneumococci, meningococci, staphylococci, gonococci, E. coli, and even the mold fungi.

What the causal focus in such conditions may be is too frequently difficult to determine, and the diagnosis must usually be made on circumstantial evidence rather than on actual proof. However, some of the more important foci operating in the body to cause these conditions can be listed as follows:

(1) The teeth. Nettleship (1879)[4] drew early attention to the association between exudative choroiditis and dental infections. However, little attention was paid to the subject until the papers of Butler (1911),[5] Lang (1913),[6] and Goulden (1914)[7] in England and Billings (1912)[8] in America. Since that time innumerable reports have appeared in the literature of cases of uveitis associated with dental infection which cleared up on removal of the infected teeth. It is to be remembered, of course, that a very large proportion of the population has gross dental sepsis without any uveitis, but these persons, it has been presumed, have developed no streptococcal ocular allergy.

(2) The tonsils. In the opinion of many recent writers, the tonsils have played a part as important as, if not more important than, the teeth, and frequently a streptococcal infection is located in both regions.

(3) The nasal sinuses. Since Ziem (1887)[9] first drew attention to the possible connection between infective conditions of the nasal sinuses and iritis, a considerable number of clinicians have recorded cases emphasizing an apparent relationship of cause and effect. The long series of cases recorded by Lang (1913),[10] de Schweinitz (1913),[11] and Goulden (1914),[7] associating iridocyclitis and choroiditis with the retention of pus in the various sinuses, drew attention to the subject.

(4) The intestinal tract. The first to draw attention forcibly to the relation between the bowel and iridocyclitis was Elschnig (1905),[12] who considered the ocular inflammation due to intoxication from products of a perverted metabolism. The researches of de Schweinitz (1906)[13] and de Schweinitz and Fife (1908),[14] however, suggested a more modern view—that any influence which the gastrointestinal tract exercised was more probably as a source of bacteria, or their toxic products, the bowel thus acting in the same manner as other foci of infection. Most authors, however, are agreed that the intestines are not a common source of infection. In this connection the undoubted influence of oral sepsis extending down and its products being absorbed from the bowel must be remembered, as witness the case of iridiocyclitis where a culture of pneumococci was grown from the feces, as reported by Browning (1912).[15]

(5) The genitourinary tract. The male genitourinary tract undoubtedly acts as an important factor in the etiology of uveitis, more especially of iridocyclitis, the most important regions being the deep urethra and the prostate. The pelvic organs in women are a source of focal infection less frequently than in the male, but their influence cannot be discounted. Brown (1934)[16] recorded cases of metastatic endophthalmitis and panophthalmitis from septic abortion and pyelitis. Terrien (1922)[17] reported a case from a prostatic abscess. A urinary infection as an etiological cause was reported by Sédan (1935).[18] The gonococcus was reported by Velhagen in 1937,[19] and Oreste (1909)[20] reported a case of E. coli as the etiological agent. In both sexes, of course, infection may arise from the urinary tract during the course of pyelonephritis, and the commonest organism responsible is E. coli (Davies, 1917, and others).[21] Levine (1930)[22] reported a case of metastatic panophthalmitis from a calculus pyonephrosis where the organism, E. coli,

was found in both the eye and the urine, and he had a similar unreported case in 1946.

Other cases of metastatic endophthalmitis have been reported from various foci of infection, such as a furuncle of the skin, in the nose, or a carbuncle of the neck by Schanz (1906),[23] Horner and Cordes (1931),[24] Higuchi (1934),[25] and Laval (1937).[26] Pneumococcus infection, first reported by Axenfeld in 1894[27] and subsequently described in detail clinically and pathologically by Bussola (1931),[28] usually occurs in the course of pneumonia but has been found in such diverse conditions as pneumococcal otitis media, cholecystitis, and coryza.

Thus it can be seen that the list of infective diseases and the organisms which may cause metastatic endophthalmitis is very large indeed and contains practically all the pyemic states. However, cases of panophthalmitis which have been proved histologically to be due to metastatic suppurative deposits have baffled ophthalmologists as to their focus of origin despite the most thorough and exhaustive investigations, both clinical and pathological (von Hippel, 1932).[29]

Before discussing the active routes of infections it is perhaps best to review the circulation of the eye. The main blood supply of the eyeball is by the ophthalmic artery, through the posterior and anterior ciliary arteries and the central artery of the retina. The central artery of the retina is given off while the ophthalmic artery is still below the optic nerve. It courses forward beneath the nerve and the sheaths until about 15 mm. from the eyeball. Here it perforates the sheaths, passes to the center of the nerve, and, proceeding to the optic papilla, divides into an ascending and descending system to supply all parts of the retina. The posterior ciliary arteries arise as two branches from the ophthalmic artery and then subdivide to form 10 to 20 short posterior ciliary arteries, which perforate the sclera around the optic nerve entrance and supply the choroid. The two long ciliary arteries perforate the sclera, one lateral and one medial to the optic nerve, and then course between the choroid and the sclera to the ciliary body and iris, giving off branches to the ciliary muscles. Upon reaching the ciliary margin of the iris, each artery sends branches upwards and downwards around the attached portion of the iris to meet with branches of the anterior ciliary artery, thus forming the major arterial circle of the iris.

It can be seen that once the central retinal artery is given off there are no connections between the central retinal artery and the posterior ciliary arteries. Thus the blood supply to the uveal tract is separate from the retinal circulation.

The route of infection is not easy to decide. In a great many cases the central artery of the retina may be the portal of entry, producing a retinitis with secondary uveitis. On the other hand, the ciliary vessels may be the portal of entry, producing a uveitis with secondary retinitis. So far as the ciliary circulation is concerned, the long or short posterior ciliary arteries may be involved, and the inflammation is at the start, and in the less dramatic cases may remain, an anterior or posterior uveitis.

Clinically, the inflammation may be classified into three types, depending upon the virulence of the infective process.

First there may be chronic uveitis which is an insidious and mild inflammatory condition. This type may be seen in the septicemia of chronic endocarditis (the ophthalmia lenta of Gilbert, 1923)[30] and in the fetus and in infants is responsible for the formation of a pseudoglioma. The mildest types, occurring in the posterior segment, have been designated septic choroiditis by Friedenwald and Rones (1930).[31]

The second type is a subacute uveitis, which sometimes remains limited to the anterior or posterior segment. The infection becomes walled off, forming an abscess. If the infection is localized in the anterior segment, a perivascular purulent infiltration of the retina may be found; if the infection is walled off in the vitreous, there may be a

diffuse infiltration of the iris with hypopyon or perhaps even a ring abscess of the cornea. These events are dependent upon the anatomy of the eye and the currents of its fluid; for the flow of the intraocular fluid causes diffusion of toxic or chemotactic substances which are liberated from the localized lesion. This usually leads to involvement of the eyeball as a whole in response to even a localized lesion. It thus can be seen that the reaction of the eye to inflammatory agents tends to a certain uniformity, with relatively little regard to the particular site at which the damaging agent first makes its appearance or produces its most intensely destructive lesion.[32]

When the infection is walled off in the posterior segment of the globe, the subsequent course is more complicated. Even if the primary localization of the infection is in the choroid, or in the retina, the organisms usually escape into the vitreous, where, free from the inhibiting influence of the tissues, they will grow in great numbers. An abscess then forms in the vitreous through the invasion of leukocytes, and this is followed by the development of granulation tissue and infiltration with mononuclear cells. Should the infection be overcome, the inflammatory mass becomes organized and converted into fibrous tissue. By this time the retina has become detached, either as a result of a subretinal, serous, or seropurulent exudate or because of the traction upon it by the shrinkage of scar tissue.

This inflammatory mass (cyclitic membrane) is confined in a pyramidal space with its base on the posterior surface of the lens and its apex pointing down the stalk of the detached retina. The ciliary processes are drawn inward along the base of the pyramid, and the epithelial cells of the ciliary body proliferate and migrate inward until they merge with the granulation tissue and are lost to recognition in the final fibrotic mass.

With the progressive contraction of the fibrous tissue in the vitreous chamber and with the failure of the disorganized ciliary body to secrete its normal quota of intraocular fluid, the eyeball becomes soft and flabby and begins to shrink, progressing on to phthisis bulbi.

The third clinical classification is that of an acute purulent panophthalmitis, in which case a localized abscess in the anterior or posterior segment of the uvea rapidly progresses to a general infection of all the tissues.

A case of this type usually starts with pain in the eye and general malaise, rise in temperature, headache, drowsiness, and sometimes vomiting. An edematous swelling, frequently with some venous engorgement, appears on the lids, particularly the upper one. An intense conjunctival and ciliary injection develops rapidly into extreme chemosis, and the cornea becomes hazy and lusterless. From an early stage, a view through the hazy cornea may be difficult. The iris is usually muddy and gray and the aqueous very turbid.

As the process advances, the intraocular contents become disorganized beyond recognition, and, if the infection is sufficiently severe, perforation of the globe and evacuation of the purulent material eventually result. There is some danger of meningitis in these cases due to the extension of the process along the sheaths of the optic nerve, or orbital cellulitis and a cavernous sinus thrombosis may develop. Accordingly, evisceration rather than enucleation is the procedure of choice in these cases to avoid these complications.

The case presented here is interesting first from the rarity of the condition and secondly because the causative organism was found by culture in the urine, the blood, and the eye. In many cases of metastatic panophthalmitis the causative organism cannot be recovered and subsequently the causative focus of infection has never been discovered. It might be added that stool culture and sensitivity determinations were also done during the patient's hospital stay and the same organism, E. coli, as noted in the case presentation, was cultured from the stool.

The patient when first seen presented a picture of an acute glaucoma. The eye was hard, but the cornea at this time was clear, as was the iris. There was no anterior chamber. It is theorized that the organisms metastasized from the kidney via the blood stream and were probably deposited in the retina via the central retinal artery. They then set up an inflammatory reaction in the vitreous which eventually caused a bulging forward of the lens and iris, obliterating the anterior chamber and creating the picture of an acute secondary glaucoma. Thus, because of the primary retinal involvement, the cornea, when the patient was first seen, was clear. The iris likewise was clear, a situation somewhat different from the usual picture of panophthalmitis or endophthalmitis when first seen. However, within several days, after the infection had had a chance to spread contiguously to the uveal tract, the iris became inflamed. Thus, on the third day after admission the iris became murky and a diagnosis of endophthalmitis could more readily be made at that time. As the infection continued, owing to its necrotizing influence on the tissues, there was a perforation of the globe. With this perforation, the patient's temperature began to fall.

Diabetics are prone to urinary tract infections, and it was theorized that the patient had, which was subsequently proved, a chronic pyelonephritic kidney which had experienced an acute exacerbation. The causative organism (E. coli) produced bacteremia, with lodgement of bacteria in the eye. This was proved by the urine, blood, and eye cultures, which all showed the same organism on culture and by sensitivity studies.

This, then, is a unique case in that the causative organism, as well as the focus of infection, was discovered, and it is presented as a case of E. coli metastatic panophthalmitis secondary to pyelonephritis.

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Vascular Lesions Affecting the Visual Pathways

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There is no better means of acquiring an understanding of the subject of neuro-ophthalmology than by firsthand examination of pathologic specimens. For the ophthalmologist it is a most enlightening experience to see the great frequency with which sections of the brain contain lesions that affect, in a variety of interesting ways, the visual pathways. The autopsy material on which this discussion is based was selected by me from a large number of brain sections inspected at the neuropathology conferences conducted by Dr. J. M. Nielsen, of Los Angeles. The present discussion will deal primarily with involvement of the visual pathways through lesions in the temporal isthmus and in the occipital lobes.

When the ophthalmologist is confronted with a cerebral defect producing a homonymous hemianopia without optic atrophy or impairment of the pupillary light reflex, he knows that the lesion is situated somewhere posterior to the lateral geniculate bodies. But for any more precise localization of the destructive process, he usually depends on such vague information as the relative congruity of the visual fields, their possible quadrantic nature, and the degree of macular sparing. Fortunately, the region between the lateral geniculate bodies and the occipital poles is, in the light of more recent neurologic findings, far less silent than has been ordinarily presumed. The presence of a homonymous hemianopia is a valuable clue that should lead to the exploration for the galaxy of other signs and symptoms which often accompany an interruption of the optic radiation. Much can be added to the diagnostic acumen of the clinician in determining the site of the vascular disturbance if he is acquainted with the nature and significance of these concomitant findings.

I. Vascular Lesions of the Temporal Isthmus

The temporal isthmus is a short and narrow passageway which constitutes the essential connection between the temporal lobe and the remainder of the brain. Through the confines of the isthmus are channelled a considerable number of nerve pathways from various portions of the brain. The temporal isthmus is bounded anteriorly by the insula and external capsule, posteriorly by the lateral ventricle, medially by the thalamus and internal capsule, and laterally it blends with the white matter of the temporal lobe. It is clinically significant that many important nerve fibers pass through the narrows of the temporal isthmus or are located adjacent to it.

An excellent description of the syndromes associated with lesions of the temporal isthmus is that written by Nielsen.* The isthmus contains the optic

Received for publication June 28, 1956.

Presented at the Annual Meeting, Pacific Coast Oto-Ophthalmological Society, Phoenix, Ariz., April 19, 1956.

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*References 1 and 2.

radiation, auditory fibers from the medial geniculate body to the transverse gyri of Heschl, fibers of the thalamoparietal peduncle, the posterior limb of the internal capsule, a portion of the external capsule, fibers of the anterior commissure, fibers of the corpus callosum, fiber pathways connecting the angular gyrus with Broca's convolution, important pathways connecting Wernicke's area and the language formulation area in the temporal lobe with Broca's convolution in the frontal lobe, and fibers from the parietal and occipital lobes to the cerebral

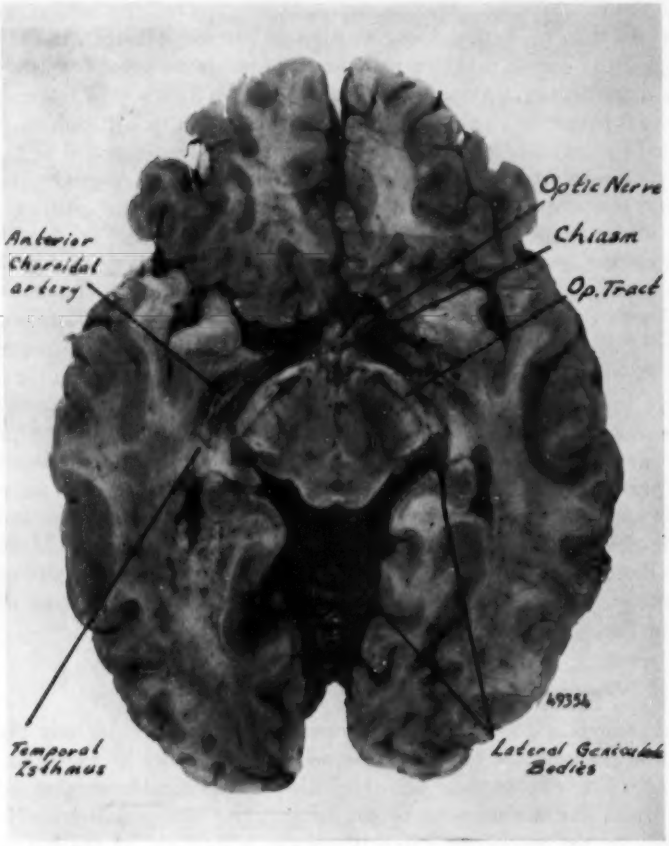

Fig. 1.—Dissection of horizontal section of the brain. Relationship of anterior choroidal artery to region of temporal isthmus is shown.

peduncles for the reflex control of the extraocular muscles. All of these important pathways are crowded in an isthmus that measures only 1 cm. in width and 1.5 cm. in length. It is therefore no wonder that vascular lesions in this compact nerve-fiber passageway produce far more neurologic disturbance than simply a homonymous defect in the visual fields. Such lesions almost completely isolate the temporal lobe from the remainder of the brain.

The blood supply of the temporal isthmus is derived primarily from the anterior choroidal artery, a branch of the internal carotid artery (Fig. 1). Thrombosis of this vessel is a fairly common source of isthmus lesion. However, not infrequently a hemorrhagic lesion in the external capsule, which is supplied by branches from the middle cerebral artery, may dissect far enough posteriorly to include the temporal isthmus in the destructive process. There is considerable

disparity between the clinical changes produced on the major side and those produced on the minor side of the brain by a lesion in the temporal isthmus.

A. Vascular Lesions in the Temporal Isthmus on the Major Side.—The nerve fibers of the optic radiation permeate the posterior limb of the internal capsule immediately after leaving the lateral geniculate body. They then pass through the temporal isthmus and thence continue toward the calcarine area in the occipital lobes (Fig. 2). A vascular lesion in the isthmus almost always produces a

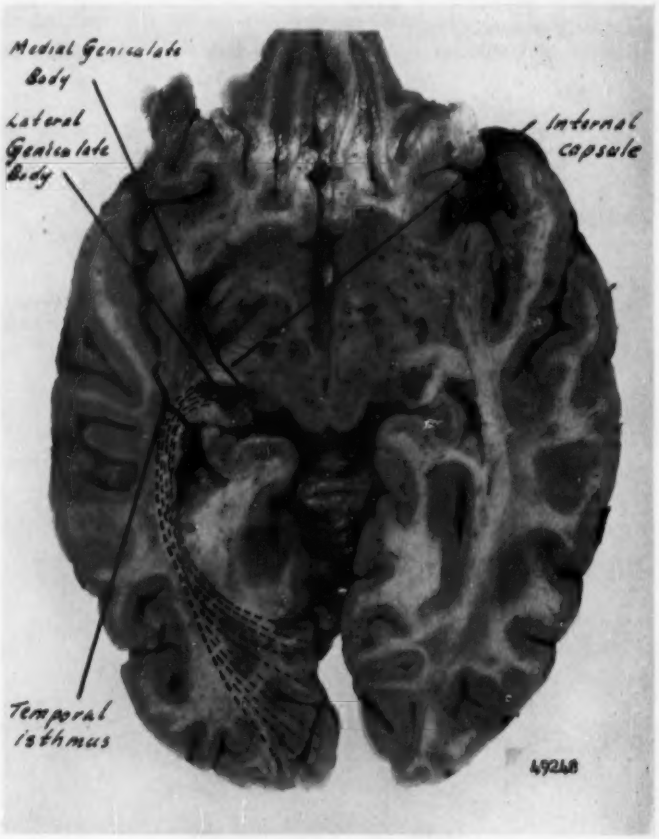

Fig. 2.—Horizontal section of brain. Course of optic radiation through posterior limb of internal capsule and temporal isthmus is demonstrated.

hemianopic type of field defect. The multiplicity of clinical findings associated with the field defects produced by involvement of the temporal isthmus on the left (major) side is illustrated by the following cases.

CASE 1 (Fig. 3).—Right homonymous hemianopia, right hemiplegia, aphasia, alexia, agraphia, conjugate deviation of the eyes to the left, and right facial weakness, all due to thrombotic softening in the temporal isthmus on the left side.

The horizontal section shows a linear area of thrombotic softening located on the left between the lenticular nucleus and the internal capsule, with extension into the temporal isthmus. The cause for the hemiplegia and homonymous hemianopia are thus obvious, since the lesion directly involves the posterior limb of the internal capsule and the optic radiation in the isthmus. The mechanism of the aphasia

requires more explanation, for it will be noted that the cerebral cortex is intact in Wernicke's sensory area for auditory perception and in Broca's motor area for speech. However, the lesion in the temporal isthmus also severed the external capsule, which is the essential route of communication between these two speech areas. This is very significant because the motor cortex in Broca's area cannot carry out the function of coordinating the muscles of speech unless it receives from the area of Wernicke and the language formulation area the proper stimulus to initiate the motor speech function. The isolation of the area of Wernicke on the major side of the brain is completed by the fact that the fibers of the corpus callosum and anterior commissure, which serve to connect areas of the first and

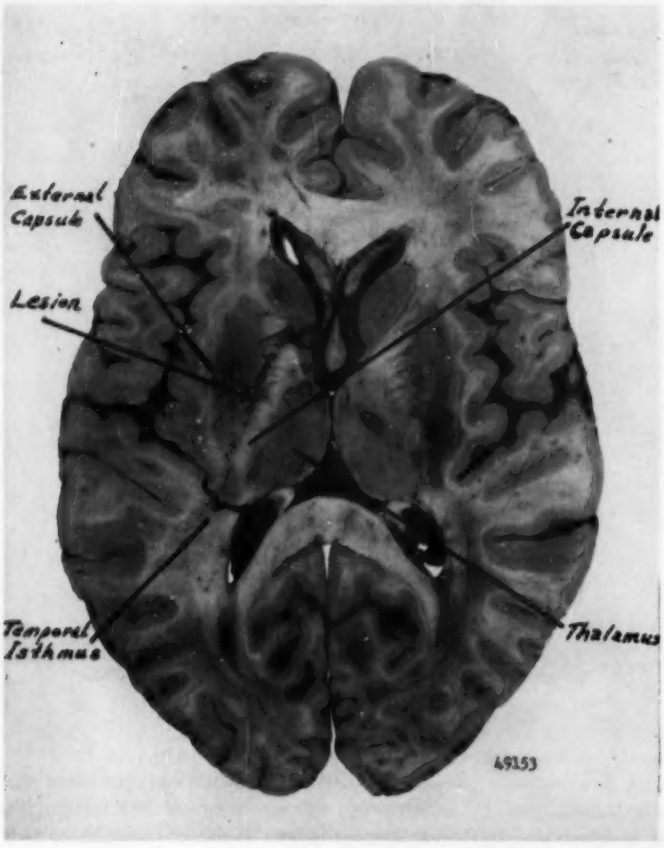

Fig. 3 (Case 1).—Brain section showing the relationship of the temporal isthmus to the external capsule, thalamus, and internal capsule.

second temporal convolutions of the left and right sides of the brain with each other, are also destroyed in their passage through the temporal isthmus. The minor area of Wernicke is usually a very inadequate substitute when aphasia is produced by lesions of this type on the major side.

An additional handicap to the patient with a lesion in the temporal isthmus on the major side is an inability to write. The angular gyrus on the major side has the function of revisualizing the symbols of written or printed language. The motor writing center in the frontal lobe requires constant communication with the

angular gyrus on the dominant side. A lesion in the temporal isthmus destroys this essential connection, and therefore the patient is unable to write.

A serious deficit in the capacity to read also accompanies a lesion of the temporal isthmus on the dominant side of the brain. Destruction of the optic radiation in the left isthmus renders the left occipital lobe functionless as far as primary visual perception is concerned. The calcarine area on the minor (right) side is probably able to convey visual impressions to the major angular gyrus through the splenium of the corpus callosum for the simple recognition of written and printed language. But the angular gyrus usually requires to and fro communication with the major area of Wernicke for the interpretation of the printed

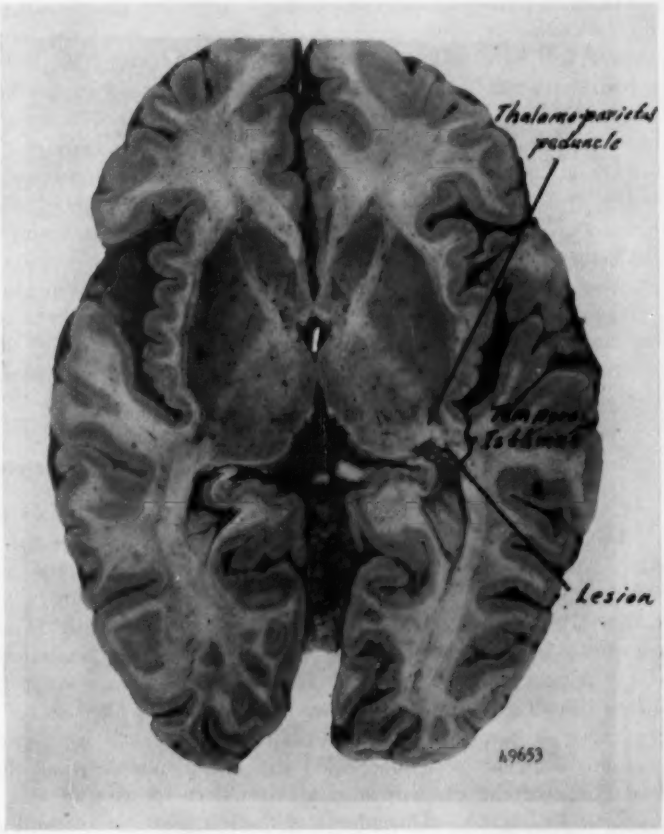

Fig. 4 (Case 2). — Thrombotic destruction in right temporal isthmus, with destruction of adjacent thalamoparietal peduncle.

and written symbols. In view of the inactivation of Wernicke's area by the lesion in the temporal isthmus, the patient is thereby rendered incapable of understanding what he can see to read.†

B. Lesions in the Temporal Isthmus on the Minor Side.—The clinical picture produced by a destructive lesion that involves the temporal isthmus on the minor side of the brain (Fig. 4) contrasts considerably with similarly located defects

† References 1 and 3.

on the major (dominant) side.[1] The absence of aphasia in such lesions on the minor side makes it possible for the patient to express his symptoms. Quite diagnostic of a right-sided isthmus lesion is a syndrome that combines a left homonymous hemianopia, left hemihypesthesia, and delusion of body scheme. The patient may state that he feels as though his left arm and leg were absent. He may fail to recognize his left extremities as part of his own body even when they are shown to him. The explanation of this is an impaired sensation on the opposite side of the body produced by involvement of the minor thalamoparietal peduncle, which is located immediately adjacent to the temporal isthmus (Fig. 4). Destruction of the sensory fibers in the posterior thalamic peduncle deprives the person of proper proprioceptive impulses from the contralateral side of the body.

If, in addition to destructive involvement of the thalamoparietal peduncle, the lesion in the minor temporal isthmus also includes the internal capsule, the patient will have hemiplegia as well. In such cases, the patient may not lack recognition of his limbs, but he may believe that they are perfectly well, in spite of their paralysis.‡ Such patients not uncommonly will attempt to walk or to move the functionless extremities on request and are unaware that the paralyzed arm or leg is completely motionless. Anosognosia or imperception of hemiplegia is the term used to designate this condition. The finding of a left homonymous hemianopia associated with left hemihypesthesia would warrant further study of the patient for evidence of delusion of body scheme, since such a syndrome localizes the causative lesion within a very precise area in the minor temporal isthmus. The presence of a left hemiplegia coupled with a left homonymous hemianopia should likewise suggest a lesion in the vicinity of the right temporal isthmus. The symptom of anosognosia would complete the picture of a destructive involvement of that region.

II. Lesions Involving the Optic Radiation in the Occipital Lobes

Case 3 (Fig. 5).—Thrombosis of both posterior cerebral arteries.

The horizontal section of the brain (Fig. 5) shows areas of softening in the region of both calcarine fissures due to thrombosis of the posterior cerebral arteries. The bilateral destruction of the areas for primary visual perception (Area 17 of Brodmann) would render the patient totally blind. The adjacent parastriate occipital cortex (Area 18 of Brodmann) depends for its function on visual sensory impulses received from Area 17. Since Area 17 was rendered inactive by the thrombotic lesions, Area 18 would likewise be functionless for the visual recognition of objects. However, Area 19 was spared, and so this portion of the occipital lobe could still be stimulated by all the other sensory modalities for the descriptive recall of objects previously seen.[6]

Case 4 (Fig. 6).—Thrombosis of the left posterior cerebral artery.

There is complete destruction of the inferior and medial surfaces of the left occipital lobe due to an old thrombosis of the posterior cerebral artery on that side. A right homonymous hemianopia would be present. The patient was described clinically as being confused and disoriented. The cause of this is seen in the pathologic specimen (Fig. 6). Areas 18 and 19 on the major side were undermined by the extensive vascular lesion. The hemianopic field defect would prove the lesser handicap as compared with the tribulations brought on by destruc-

‡ References 4 and 5.

tion of the secondary and tertiary cortical areas. The lesion in the major Area 18 in a strongly left-brained patient would deprive him of the ability to recognize objects. A further complication in this case was the concomitant involvement of Area 19, and so the power to revisualize was also deleted. Thus the patient would be lost in his own house for lack of capacity to recall spatial relationships.[7] The memory patterns stored in Area 19 for knowledge of directions could no longer be drawn upon; consequently, the patient would be unable to determine the location of streets or buildings or any of the fundamental characteristics of objects formerly very familiar to him.

Fig. 5 (Case 3). — Thrombosis of both posterior cerebral arteries.

A comparison of the neurologic changes produced by the thrombotic lesions in the first and second cases of this series presents an interesting discussion. In Case 1 both occipital lobes were extensively damaged. Clinically the patient was totally blind. This handicap was mitigated by the fact that Area 19 was spared. Being thus able to revisualize and recall, the patient was spared the confusion and disorientation that plagued the second patient. In Case 2 the area of destruction involved the left occipital lobe alone, but it included all of Areas 17, 18, and 19. The visual impairment consisted of a right homonymous hemianopia. This would appear a considerably less visual loss than the total blindness suffered by

the patient in Case 1. However, of paramount significance is the fact that the vascular lesion in Case 2 destroyed the major (dominant) occipital lobe. Even though the patient retained sight in the homonymous half fields of each eye, the destruction of Area 18 in a strongly left-brained person rendered him incapable of recognizing objects. Added to that was the loss of Area 19, which left him greatly confused and disoriented because of lack of ability to visualize the location of landmarks, the direction of streets, or the characteristics of persons and places that formerly were well known to him.

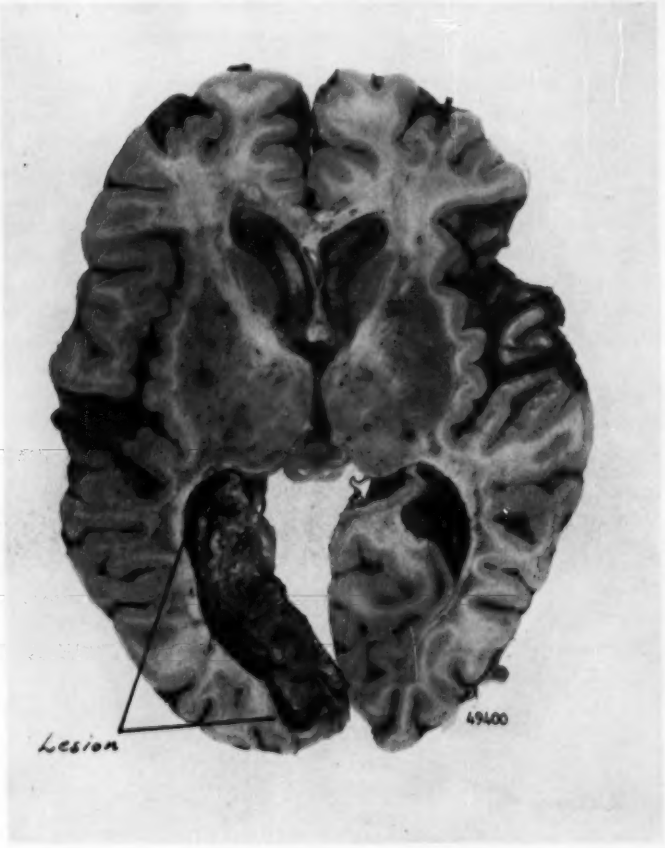

Fig. 6 (Case 4). — Thrombosis of left posterior cerebral artery.

CASE 5 (Fig. 7).—Hemorrhagic lesion in left occipital cortex.

This lesion severed the optic radiation on the left and destroyed the major Areas 18 and 19. Clinically the patient would show a right homonymous hemianopsia. Disorientation in space would accompany such a lesion, primarily because of the inability of the patient to recall the direction or position of landmarks previously commonplace to him. A more localized destructive lesion in the lower portion of Area 18 on the major side in a predominantly left-brained person may have the selective effect of depriving the patient of the capacity to recognize inanimate objects, while animate objects remain familiar to him. Contrariwise, a selective lesion in the upper portion of the convex surface of Area 18 on the dominant

side may permit recognition of inanimate objects but the patient may be unable to recognize all animate objects. The friends who visit such a patient may be totally unfamiliar to him except through such other sensory media as the sound of their voices.

CASE 6 (Fig. 8).—Thrombosis of the right posterior cerebral artery with softening in the temporal isthmus and forceps major.

Clinically, a left homonymous hemianopia was found. At autopsy an area of thrombotic softening involved the right temporal isthmus and thus accounted

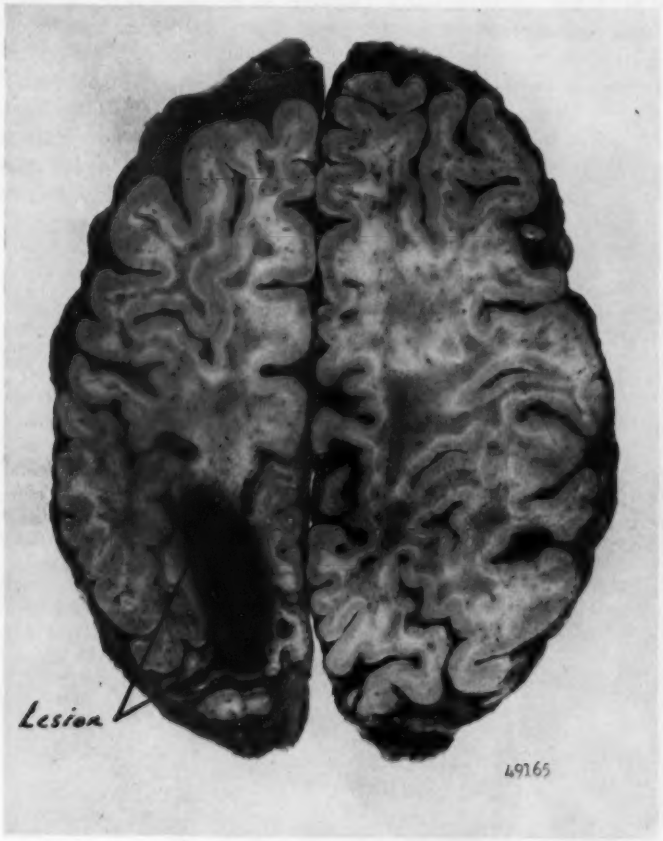

Fig. 7 (Case 5).—Hemorrhage in left occipital cortex.

for the left homonymous hemianopia. The destructive lesion also severed the forceps major on the right. Had the lesion in the splenium occurred alone, an interesting interruption in the communication between major and minor occipital lobes would have occurred. In most right-handed persons, with dominant left brains, the visual impulses from the minor (right) Area 17 must first be conveyed to the adjacent Area 18 and thence through the splenium of the corpus callosum to the major Area 18 before the recognition of familiar objects can be accomplished. Interruption of the splenium by a lesion such as that shown in Figure 8 prevents the major Area 18 from bringing to consciousness the visual impressions from the calcarine cortex of the opposite (right) occipital lobe. The consequence is visual agnosia for objects in the left homonymous half fields.

Comment

In vascular lesions posterior to the lateral geniculate bodies the essential ocular involvement is a homonymous hemianopia. This finding contributes little in itself to the determination of the site of the destructive process. However, such field defects should always call for a thorough search for the concomitant neurologic signs and symptoms which often have localizing value. The site of the cerebral lesion can often be determined with considerable accuracy if the observer is sufficiently acquainted with the syndromes that characterize involvement of various portions of the visual pathways.

Fig. 8 (Case 6). — Thrombosis of the right posterior cerebral artery, with softening in the temporal isthmus and forceps major.

The temporal isthmus is a narrow nerve-fiber channel which connects the temporal lobe with the remainder of the brain. Lesions of the isthmus on the left (major side) produce not only a right homonymous hemianopia but aphasia, agraphia, alexia, and, often, right hemiplegia. The finding of left homonymous hemianopia, left hemihypesthesia, and delusion of body scheme usually pin-points the lesion in the right temporal isthmus and adjacent thalamoparietal peduncle. Imperception of hemiplegia (anosognosia of Babinski) occurs from lesions involving the right internal capsule in this area.

Occlusion of one or both posterior cerebral arteries is a relatively common finding at autopsy. An understanding of the function of Areas 18 and 19 of Brodmann contributes much to the examiner's acumen in localizing destructive lesions in which a homonymous hemianopia might otherwise be the only apparent finding.

Confusion and disorientation often accompany lesions of Area 19 on the dominant side because the patient is deprived of the ability to revisualize and recall. Memory is to a large extent a visual process, for Area 19 is utilized to form the mental picture of objects previously seen. When the memory patterns stored in Area 19 for knowledge of direction cannot be drawn upon by the various senses, the patient cannot recall the location of streets and buildings and he may be lost in his own house. As described in the cases presented, a patient with complete blindness from bilateral destruction of Areas 17 and 18 may be less handicapped than another patient with only a lesion in Area 19 on the dominant side, for the associated disorientation may prevent the latter patient from utilizing efficiently the vision preserved in his homonymous half fields.

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Elaboration of Bicarbonate Ion in Intraocular Fluids

I. Aqueous Humors, Following Intravenous Infusion of Sodium Bicarbonate

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The dominant thinking prevailing with regard to the understanding of the dynamic properties of the aqueous humor arose chiefly from the classic experiments of Friedenwald and co-workers [1] and matured later in the form of the secretion-diffusion theory postulated by Kinsey.* Thus, hydroxyl ions are presumed to be generated continuously by the oxidation of reduced cytochrome oxidase in the epithelium of the ciliary processes. Neutralization of the hydroxyl ions by carbon dioxide is postulated as the source of the bicarbonate ion, which then diffuses into the posterior chamber, resulting in the excess of bicarbonate ion in this fluid compared with that in blood plasma. The net dynamic effect of such a distribution is considered responsible for the hypertonicity (equivalent to 3 mM. NaCl/liter) of the aqueous humor of the rabbit eye and the associated osmotic flow of fluid into the eye. The physiologic interplay of the forces responsible for the inflow of fluid or the formation of aqueous humor and those forces which control the mechanism of outflow, chiefly at the iris angle, serves to regulate the intraocular pressure. Although the basic formulation of the way in which the cytochrome oxidase system is presumed to participate in the elaboration of the bicarbonate ion has been recently questioned on theoretical grounds,[4] the concept of the pivotal role of the bicarbonate ion in the formation of aqueous humor has adequately served as a basis for our understanding of the dynamics of aqueous humor.

Notwithstanding the fact that the bicarbonate ion concentration in the aqueous humor is significantly higher than that in the blood plasma, direct experimental evidence for the belief that it is secreted or actively transported into the posterior chamber by the cellular activity of the ciliary processes is lacking. It seemed reasonable that a better understanding of the mechanism of the elaboration of bicarbonate ion in intraocular fluids might be achieved by studying the relationship between the bicarbonate ion concentration in the blood plasma and that in the aqueous humor. This paper is a report of the results of such a study.

Procedure

Unanesthetized adult pigmented rabbits weighing between 4 and 6 lb. were used. The procedures for the withdrawal of aqueous humor from the anterior and posterior chambers and the analysis of the bicarbonate ion concentration have been described.[5] All samples of blood plasma were prepared from whole blood withdrawn from the ear artery into a heparinized syringe.

Received for publication June 11, 1956.
Supported in part by a grant-in-aid from the National Council to Combat Blindness.
Department of Research, Wills Eye Hospital, and Department of Physiological Chemistry, Graduate School of Medicine, University of Pennsylvania.
* References 2 and 3.

Continuous Intravenous Infusion.—The animals were confined in wooden boxes fitted with an opening in the top to permit only the head and ears to protrude. The 1.3% $NaHCO_3$ solution was administered through the usual venoclysis assembly at a speed of about 6 to 8 ml/10 minutes (15 to 20 drops/minute). Connection with the ear vein was prepared as follows: Polyethylene tubing, PE 50, was inserted a distance of about 1 in. into the marginal ear vein, previously punctured with a 21-gauge needle. The other end of the tubing was tightly fitted with a 21-gauge needle 1½ in. long and connected to a syringe. Patency of the vein was checked by injecting about 1 ml. of isotonic saline solution. The hypodermic needle customarily connected to the venoclysis assembly was removed by cutting the plastic tube just behind it. The tapered end could then very easily replace the syringe and provide a tight and direct connection through the 21-gauge needle with the polyethylene tubing in the vein. The rate of flow was adjusted by means of a Hoffman screw clamp and timed with a stop watch. Care was taken to maintain a rather constant rate of flow during the course of the experiment. All withdrawals of fluid at the indicated time periods were done without interrupting the intravenous feeding.

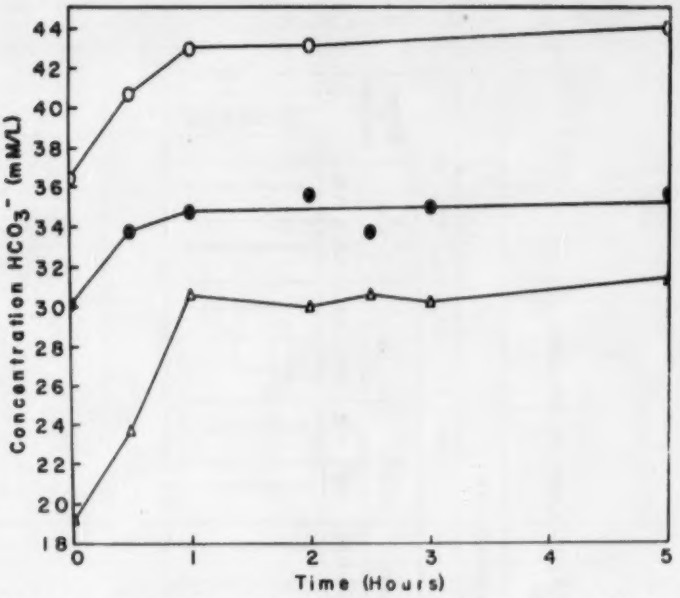
The intraocular pressure of the anesthetized rabbit eye was measured with a Schiøtz tonometer, with use of a 5.5 gm. weight. Tonography was performed with a Mueller Electronic Tonometer, and tracings were recorded on a Leeds and Northrup Speedomax recorder. Constant voltage was maintained by a voltage regulator, as described by Askovitz.[6] At least 24 hours separated the carrying out of tonography on the animals as controls and on the same animals under the experimental conditions. Both eyes were used in all cases. Since steady-state conditions obtained after one hour, tonography was performed in all cases two to three hours after the start of the infusion. The animals were immobilized for tonography by wrapping in a suitably prepared towel. However, it was found very difficult and inadvisable to keep the animal enclosed for such a long period of time. Accordingly, the towel was slipped over the animal's head and ears and gathered together and tied loosely in front of his body. Under these conditions the intravenous infusion could be conducted in the much more comfortable rabbit box. About 15 minutes before tonography the animal was carefully removed from the box and the towel was wrapped around the animal securely without interrupting the feeding. Under these conditions tonography could be carried out with a minimum of discomfort to the animal and with little chance of interfering with the constant rate of intravenous infusion.

The results are summarized in Table 1 and are graphically presented in the Figure. Because of the difference in time in which the experiments were done, different animals were used for the anterior chamber taps and the posterior chamber taps. In the experiments in which the aqueous humor from the anterior chamber was analysed, the fluid from both eyes was used, and the value in the Table is an average of the two. The zero-minute data for the blood plasma and the aqueous humor of the anterior chamber represent average values of 95 animals previously obtained in our laboratory. In the experiments in which the aqueous humor from the posterior chamber was analysed, samples of blood plasma and aqueous humor from one eye were analysed at zero minutes and again at the indicated time period. The zero-minute data represent the average of all such values for these experiments. Finally, since the data for the concentration of bicarbonate ion in the blood plasma for the same time periods in the two sets of experiments were practically the same, the average values were used in the Figure.

TABLE 1.—*Summary of Results: Effect of Intravenous Infusion of 1.3% $NaHCO_3$ on HCO_3^- in Aqueous Humor*

	HCO_3^-, mM/L.													
	0 Min.		30 Min.		60 Min.		120 Min.		150 Min.		180 Min.		300 Min.	
	Pl.*	A.H.†	Pl.	A.H.	Pl.	A.H.	Pl.	A.H.	Pl.	A.H.	Pl.	A.H.	Pl.	A.H.
A. Anterior chamber														
Av.	19.4	30.1	23.7	33.8	31.0	34.8	31.2	35.6	30.6	33.7	30.2	35.0	30.5	35.6
S. D.	5.3	3.6	1.5	1.1	2.6	3.0	3.0	3.7	2.8	2.9	2.4	1.8	1.5	2.3
Samples, No.	95	95	5	5	6	6	6	6	6	6	6	6	6	6
B. Posterior chamber														
Av.	19.1	36.5	23.7	40.7	30.1	43.0	28.7	43.1					32.3	44.1
S. D.	3.3	3.2	1.5	1.4	3.3	5.9	2.6	3.9					3.6	4.3
Samples, No.	26	26	5	5	7	7	6	6					8	8
	Av.	S.D.	Av.	S.D.	Av.	S.D.	Av.	S.D.	Av.	S.D.	Av.	S.D.	Av.	S.D.
C. Ratio‡														
A. C./Pl.	1.55	0.37	1.43	0.10	1.13	0.11	1.14	0.13	1.10	0.10	1.17	0.12	1.13	0.07
P. C./Pl.	1.91	0.42	1.72	0.06	1.48	0.23	1.50	0.08			(1.45)§		1.37	0.18
P. C./A. C.	1.21		1.20		1.28		1.21				(1.24)§		1.24	

* Arterial blood plasma.
† Aqueous humor.
‡ A. C., anterior chamber; P. C., posterior chamber.
§ Interpolated from curves.



Bicarbonate ion concentration, mM/liter, following intravenous infusion of 1.3% $NaHCO_3$; -Δ-Δ-Δ-, arterial blood plasma; -•-•-•-, aqueous humor of anterior chamber; -O-O-O-, aqueous humor of posterior chamber.

Results

The results show that the bicarbonate ion concentration of the plasma rose uniformly during the first 60 minutes and then remained steady at a level of 30 to 31 mM/liter for the next 4 hours. The concentration in the anterior chamber aqueous humor rose less rapidly during the first 60 minutes and then remained rather steady at about 35 mM/liter for the next 4 hours. The bicarbonate ion concentration of the aqueous humor in the posterior chamber also did not rise as fast as that in the blood plasma, but it reached a new level (43 mM/liter) in 60 minutes which remained steady during the next 4 hours, at the end of which time the concentration was 44.1 mM/liter. The relative rates of increase and the levels of bicarbonate ion concentration in the different fluids are expressed in Table 1 under Ratio. It is at once apparent that although the bicarbonate ion concentration of the blood plasma rose faster than that in the aqueous humor of both chambers and reached a proportionately higher level, the ratio of the bicarbonate ion concentration in the posterior chamber to that in the anterior chamber was constant throughout the experiment.

The effect of the intravenous infusion of 1.3% $NaHCO_3$ upon the intraocular pressure of the rabbit eye is described in Table 2. It is apparent that the experimental treatment had no appreciable effect upon the intraocular pressure for at least three hours. The results of experimental tonography, Table 3, confirm this observation. It is also apparent that the experimental conditions had no significant effect upon the facility of aqueous outflow. The left and right eyes of the controls

TABLE 2.—*Effect of Intravenous Infusion of 1.3% $NaHCO_3$ upon the Intraocular Pressure of Rabbit Eye*

Time, Min.	Schiøtz Readings with 5.5 Gm. Wt.																Average of Readings
	Animal No.																
	1 (5¾)*		2 (5½)		3 (5)		4 (6)		5 (8¼)		6 (7¼)		7 (6)		8 (6½)		
	O.S.	O.D.	O.S.	O.D.	O.S.	O.D.	O.S.	O.D.	O.S.	O.D.	O.S.	O.D.	O.S.	O.D.	O.S.	O.D.	
0	3	4	4	4	5	5	4	5	4	4	4	3	4	4	3	4	4.0
20	3	3	4	3	3	4	5	4	3	4	5	5	2	3	3	4	3.8
40	3	3	4	5	3	3	4	5	3	3	6	5	3	2	4	5	3.8
60	4	3	3	5	4	3	5	3	4	4	3	2	3	3	5	4	3.6
80	3	2	3	4	3	4	5	5	3	2	4	5	4	3	4	4	3.6
100	4	3	3	3	5	4	4	3	5	3	2	4	3	4	5	3	3.6
120	2	3	4	3	4	5	2	3	5	4	3	3	2	4	4	3	3.4
150	3	4	4	4	4	5	3	4	3	4	5	3	2	4	2	2	3.5
180	4	3	4	5	4	3	4	3	5	3	--	--	4	4	3	4	3.8

* Weight of the animal, in pounds, is given in parentheses.

TABLE 3.—*Effect of Intravenous Infusion of 1.3% $NaHCO_3$ upon Tonography of Rabbit Eyes**

Rabbit		Control		Experimental	
		P_1†	C_1‡	P_2	C_2
1	O.S.	21	0.19	17	0.18
	O.D.	25	0.22	19	0.26
2	O.S.	19	0.16	19	0.24
	O.D.	23	0.17	20	0.26
3	O.S.	22	0.31	24	0.19
	O.D.	20	0.20	38	0.08
4	O.S.	26	0.24	25	0.22
	O.D.	22	0.18	29	0.30
5	O.S.	25	0.08	21	0.16
	O.D.	20	0.07	26	0.23
6	O.S.	19	0.14	20	0.14
	O.D.	23	0.16	22	0.17
Average	O.S.	22.0			
	O.D.	22.2			
Total av.		22.1	0.18	23.8	0.20
S. D.		2.3	0.06	5.4	0.06

* At least 24 hours intervened between control and experimental tonography on the same rabbit.
† Introcular pressure in millimeters of Hg.
‡ Coefficient of aqueous outflow, microliters per minute per millimeter Hg.

are compared to show that tonography in one eye had no significant effect upon the other eye.†

Comments

At the inception of this investigation it was arbitrarily decided to raise the bicarbonate ion concentration of the blood plasma to the value of the normal aqueous humor of the rabbit eye (30 to 31 mM/liter) and to maintain it at this level for varying periods of time. Under the experimental conditions described it was found that some animals did not show a rise in the bicarbonate ion concentration in the blood plasma and in the aqueous humor. Apparently they were capable of excreting the excess $NaHCO_3$ as fast as it was being administered. Preliminary results indicated that when the bicarbonate ion concentration of the blood plasma rose to not less than 26.5 mM/liter, after 60 minutes or longer, the concentration in the aqueous humor also rose. Below this level the rise in the bicarbonate ion concentration in the aqueous humor was erratic and irregular. Consequently, unless the concentration of bicarbonate ion in the blood plasma reached a value of at least 26.5 mM/liter after 60 minutes or longer the experiment was discarded. As for the 30-minute period, the value of 23 mM/liter was set as the lower acceptable limit, provided the initial blood value was about 20 mM/liter or less. From the above discussion it is reasonable to conclude that the experimental conditions described are so mild as just to exceed the capacity of the animal to resist the change.

† Kornbluth and Linner (A. M. A. ARCH. OPHTH. 54:717, 1955) observed that the intraocular pressure and rate of flow of aqueous humor were slightly higher in the eye upon which tonography was first performed. The coefficient of aqueous outflow, however, was the same in both eyes.

Discussion

A consideration of the curves in the Figure indicates that the bicarbonate ion concentrations in the aqueous humors vary directly with increasing concentrations in the plasma. When the concentration in the plasma is steady, as during the interval from one to five hours, the concentrations in the aqueous humors are also constant. Whether the concentrations in the aqueous humors reach maximum levels regardless of the increase in concentration in the blood plasma, as is the case with ascorbic acid,[7] has not been determined.

It is perhaps significant, however, that the values under Ratio in Table 1 indicate that the rise in bicarbonate ion concentration in the plasma (55%) after the first hour is greater than that in the aqueous humor of the anterior (16%) and posterior chambers (18%) and that the steady state level attained is also proportionately higher (ratios of 1.1 to 1.2 for anterior chamber fluid to plasma and 1.4 to 1.5 for posterior chamber fluid to plasma compared with the originial ratios of 1.55 and 1.91, respectively). These results suggest that under the experimental conditions increases in the concentration of bicarbonate ion in the plasma are not completely reflected in directly proportional increases in the concentration in the aqueous humors, but that some other factor besides the level in the plasma contributes to the regulation of the bicarbonate ion concentration in the aqueous humors. Moreover, it seems reasonable to conclude that the active transport mechanism or mechanisms presumably operating to maintain the concentration of bicarbonate ion in the aqueous humors in excess of that in the plasma are dependent, in part, upon the level of bicarbonate ion in the latter.

Concerning the route of entry of the bicarbonate ion into the intraocular fluids, it is of interest to evaluate the experimental results by the theoretical equations of Kinsey and Palm.[8] To express the rate of change of concentration of the test substance in the anterior chamber, Kinsey and Palm have used the equation

$$\frac{dCa}{dt} = K_F(C_p - C_a) + K_D(C_b - C_a) \qquad (1)$$

where C_p, C_a, and C_b represent, respectively, the concentrations of test substance in the posterior chamber, in the anterior chamber, and in the blood plasma. K^F represents the rate of flow per minute as a fraction of the volume of anterior chamber; K^D represents the rate of diffusional exchange per minute between anterior chamber and blood plasma expressed as a fraction of the concentration gradient. Thus, the rate of change of anterior chamber concentration, $\frac{dCa}{dt}$, is expressed as the algebraic sum of inflow from the posterior chamber ($K^F C_p$), outflow at the angle ($K_F C_a$), and diffusional exchange K_D ($C_b - C_a$). Under conditions of steady-state where $\frac{dCa}{dt} = 0$, equation (1) becomes $\frac{K_F}{K_D} = \frac{C_a - C_b}{C_p - C_a}$ (2)

If equation (1) adequately describes the main factors involved in accumulation of bicarbonate ion in the anterior chamber, then by substituting steady-state values in equation (2) one should obtain an estimate of the ratio of $K_F:K_D$. Furthermore, if the individual coefficients do not change under the experimental conditions, the ratio should also remain constant. Applying these considerations to the experimental data, it is found that at zero minutes the ratio of $K_F:K_D$ equals 1.67, while under the steady-state conditions after one hour and up to five hours of intravenous feeding of isotonic $NaHCO_3$ the ratio has decreased

to 0.51. Because of the insufficient number of experimental points in the first hour, neither K_D nor K_F could be determined by the method of Kinsey and Palm [8] or Friedenwald and Becker.[9] Nevertheless, protein analysis of the aqueous humor indicated that the experimental treatment had no apparent effect upon the permeability of the blood aqueous barriers. On the other hand, if it is assumed that a reduction in the rate of flow of aqueous humor was responsible for the decrease in the ratio of the coefficients, then one might expect to find a reduction in the intraocular pressure. The results in Table 2 show that under the experimental conditions the introcular pressure was unaffected. In this connection the possibility exists that the expected decrease in intraocular pressure associated with a decrease in the rate of flow of aqueous humor is prevented by a compensatory increase in the resistance to aqueous outflow, similar to that reported by Becker and Constant [10] in some acetazoleamide- (Diamox-)treated animals. The results of tonography given in Table 3 not only support the Schiøtz findings that the intraocular pressure is unchanged but also show that the experimental conditions had no significant effect upon the ease with which the aqueous humor flows out of the eye.

The results of this investigation, therefore, suggest that the source of the bicarbonate ion in the aqueous humor of the anterior chamber is not adequately defined by the current concepts based upon diffusional exchange with the blood and the difference between the quantities entering by flow from the posterior chamber and leaving by flow at the angle.

The significance of the constancy of the ratio of the bicarbonate ion concentration in the posterior chamber to that in the anterior chamber, under the experimental conditions, relative to an understanding of the factors responsible for its elaboration, is not clear at present.

Summary

$NaHCO_3$ (1.3%) was administered intravenously to adult pigmented rabbits, 4 to 6 lb., over a period of five hours. Bicarbonate ion concentrations in the anterior and posterior chambers and in the arterial blood plasma were determined at varying periods.

The bicarbonate ion concentration in the plasma rose from 20 to 30 mM/liter in 60 minutes and remained steady for the next 4 hours; that in the anterior chamber rose from 30 to 35 mM/liter in the same time period and also remained steady for the next 4 hours; similarly, the bicarbonate ion concentration in the posterior chamber rose from 36 to 44 mM/liter.

While the ratio of the bicarbonate ion concentration in the aqueous humors to that in the blood plasma decreased, the ratio of concentration in the posterior chamber to that in the anterior chamber was constant at 1.2 to 1.3.

The experimental conditions had no effect upon the intraocular pressure or upon the facility of aqueous outflow.

It is concluded that the source of the bicarbonate ion in the anterior chamber aqueous humor is not completely defined by the current concepts based upon diffusional exchange with the blood and the difference between the quantities entering by flow from the posterior chamber and leaving by flow at the angle.

Dr. Irving H. Leopold, Director of Research, gave encouragement and helpful discussion during the course of this investigation, and Dr. S. S. Ahmad, Surg. Lt. Cmdr., Pakistan Navy, performed the experimental tonography.

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Elaboration of Bicarbonate Ion in Intraocular Fluids

II. Vitreous Humor, Normal Values

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The vitreous humor is considered to be an important reservoir in the diffusional exchange of substances with the aqueous humor of the posterior chamber. Indeed, Christiansson and Palm [1] and Kinsey and Palm,[2] as well as Friedenwald and Becker,[3] have shown that failure to take into account the dynamic properties of the chemical components of the vitreous humor in diffusional exchange with those in the aqueous humor leads to inaccurate estimates of the rate of flow of aqueous humor. Furthermore, determination of the distribution of substances in the different sections of the vitreous humor gives some idea as to the routes by which they enter. Thus, Duke-Elder and Davson,[4] by a modification of the technique employed by Adler,[5] concluded from the uniform distribution of glucose in the vitreous humor under normal conditions and when the blood sugar level was high that glucose diffuses into the vitreous humor of a cat throughout the entire posterior segment of the eye from the uveal, choroidal, and retinal vessels, rather than from the posterior chamber aqueous humor alone. A similar route of entry was shown by Davson and co-workers [6] to exist for urea and thiocyanate. From the results of experiments with radioactive sodium and potassium ions they also suggested that, since there was a gradation in concentration from the anterior to the posterior section of the vitreous humor, these ions penetrate predominantly from the ciliary body and iris areas and that penetration from the choroid and retinal circulation was comparatively small.

Because of the important role that the bicarbonate ion is believed to play in the formation of aqueous humor and in the maintenance of intraocular pressure, it was considered desirable to determine the distribution of the ion in the vitreous humor and to correlate this with the concentration in the blood plasma and aqueous humors of the anterior and posterior chambers. This paper represents a determination of the normal distribution of bicarbonate ion in the vitreous humor of the rabbit eye. In another paper [7] the effect of raising the bicarbonate ion concentration in the blood upon that in the vitreous humor will be reported.

Procedure

Pigmented rabbits weighing between 4 and 6 lb. were used in all experiments. The animals were killed by air embolism and placed in an upright position for one to one and one-half minutes to allow drainage of blood from the ocular vessels. The eyes were immediately enucleated and placed in a tube surrounded

Received for publication June 11, 1956.

This investigation was supported in part by grant-in-aid from the National Council to Combat Blindness.

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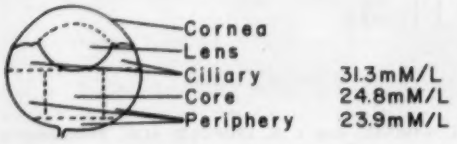
by a mixture of solid CO_2 in acetone. The frozen eyes were sectioned in the following manner in order to obtain the sections of vitreous humor indicated in the Figure: The posterior cap was removed and the vitreous was scooped out and



Bicarbonate Concentration of Vitreous Humor

collected in a conical centrifuge tube. A cut was then made just behind the lens (approximately 5 to 6 mm. from the corneal-scleral limbus), and the vitreous humor adjacent to the ciliary body was scooped out and collected in another conical centrifuge tube. This section is referred to as "ciliary." In all cases the vitreous humor lying between the plane of the posterior lens capsule and the cut was removed and added to the corresponding section of vitreous humor. Furthermore, in removing the vitreous humor from the ciliary body area care was taken not to contaminate this with any posterior chamber aqueous humor. The central core of the vitreous humor ("core") was removed by means of a brass cork borer, size No. 7, approximately 10 mm. inside diameter. The remaining vitreous humor was added to that from the posterior cap and called "periphery." The entire procedure of collecting the various sections usually took less than three minutes, and little difficulty was encountered with thawing of the samples during removal. In some cases after removal of the vitreous humor adjacent to the ciliary body the rest of the substance was collected as a whole and referred to as "rest." Where the whole vitreous humor was analysed, both sections were mixed together and the bicarbonate ion concentration determined on suitable aliquots. Whenever necessary the sections were centrifuged to remove pigment or cellular debris.

Analysis

The bicarbonate ion concentration was determined in a Warburg apparatus, as previously described for aqueous humor and blood plasma.[8] This method as checked with standard bicarbonate solutions is accurate to within 5%. Duplicate analyses were performed on 0.1 to 0.2 ml. samples.

Results

Bicarbonate ion concentration. The results are presented in the Table and summarized diagrammatically in the Figure. The values in parentheses in column "rest" were calculated from the corresponding values for "core" and "periphery." The results show that the bicarbonate ion concentration of the total vitreous humor of the rabbit eye is 25.3 (S. D. 1.8) mM/liter; ciliary body area, 31.3 (S. D. 3.5) mM/liter; core, 24.8 (S. D. 2.1) mM/liter; periphery, 23.9 (S. D. 1.9) mM/liter, and the rest, 24.0 (S. D. 2.6) mM/liter. The bicarbonate ion concentration in the area of the ciliary body is, therefore, 34% higher than that in the rest of the vitreous humor.

Bicarbonate Concentration of Rabbit Vitreous Humor

	Whole Vitreous, mM/L.	Ciliary, mM/L.	Core, mM/L.	Periphery, mM/L.	Rest,* mM/L.	Ciliary/Rest, mM/L.
	27.9	32.9	24.2	23.1	(23.6)†	1.39
	27.6	30.0	20.4	19.7	(20.1)	1.49
	23.9	32.3	24.5	25.1	(24.8)	1.30
	23.2	34.3	27.0	25.1	(26.1)	1.32
	23.3	30.1	27.5	27.4	(27.4)	1.10
	25.0	35.3	25.3	24.5	(24.9)	1.42
	24.0	31.6	22.4	23.5	(22.9)	1.38
	27.6	25.0	24.1	24.0	(24.1)	1.45
	22.4	37.6	....	....	19.8	1.90
	23.6	26.2	....	....	24.3	1.08
	27.1	21.5	....	....	27.6	0.78
	23.7	34.1	....	....	19.0	1.79
	26.9	32.4	....	....	22.1	1.47
	26.3	29.7	....	....	28.2	1.05
	26.8	28.5	....	....	20.5	1.39
	25.4	31.7	....	....	24.4	1.30
	....	29.2	27.4	22.6	(23.0)	1.27
	....	30.9			26.5	1.17
Av.	25.3	31.3	24.8	23.9	24.0	1.34
S. D.	1.8	3.5	2.1	1.9	2.6	0.25

* Rest=core+periphery.
† Values in parentheses calculated from corresponding values for core and periphery.

Volume relations of sections. The average volume of the total vitreous humor of 45 rabbit eyes was 1.47 ml. (S. D. 0.22 ml.); that of the ciliary body area was 0.54 ml. (S. D. 0.17 ml.), and that of the rest of the vitreous humor, 0.93 ml. (S. D. 0.15 ml.).

Comments

The bicarbonate ion concentration of the vitreous humor of the rabbit eye (25.3 mM/liter) lies between that of the blood plasma (average, 19.4 mM/liter) and that of the aqueous humor (30.1 mM/liter) in anterior chamber and in posterior chamber (36.0 mM/liter).* On the basis of the higher concentration in the area adjacent to the ciliary body (31.3 mM/liter) compared with that in the peripheral ring (23.9 mM/liter) and central core (24.8 mM/liter) it is reasonable to assume that the rate of entry into the ciliary area is higher than that into the rest of the vitreous humor. Since the most anterior section of the vitreous humor is adjacent not only to the ciliary body but also to that section of the lens immediately posterior to the equator and extending back to within the area of the posterior pole, one can not decide, on the basis of the results, the immediate source of the higher bicarbonate ion concentration in this section of the vitreous humor. The fact that the concentration in the central core is not significantly higher than that in the peripheral ring, but is equal to it, would suggest that the contribution to the bicarbonate ion concentration from the most posterior aspect of the lens capsule and cortex does not exceed that from the choroidal and retinal vessels. Conversely, the choroidal and retinal circulation can not be considered as a sole source of the bicarbonate ion for the vitreous humor behind the ciliary body and lens, since, if this was so, because of the unfavorable volume area relation of the central core relative to that of the peripheral ring, one would expect to find the concentration in the peripheral ring

* During the preparation of this paper a report[9] appeared indicating that bicarbonate ion concentration of the vitreous humor (19.5 mM/liter) is lower than that of the blood plasma (25.6 mM/liter) and that of the aqueous humor (27.7 mM/liter).

higher than that in the central core. This is contrary to what actually exists. Similarly, if the bicarbonate ion is assumed to diffuse from the aqueous humor of the posterior chamber into the vitreous environment, this might explain the relatively high concentration in the vitreous humor immediately behind the posterior chamber. However, unless the rate of diffusion of bicarbonate in the ciliary area of the vitreous humor into the uveal capillaries is faster than the diffusion from the posterior chamber into the vitreous humor, one would expect the bicarbonate to continue to diffuse from the ciliary area into peripheral ring of the vitreous body. Such a diffusion would give rise to a concentration gradient from ciliary body area to peripheral ring to central core. This, of course, does not obtain.

It is, therefore, apparent that no definite conclusions can be drawn concerning the route of entry of bicarbonate ion into the vitreous humor from a knowledge only of the distribution of the ion in that fluid.

Summary

Determination of the bicarbonate ion concentration in frozen sections of the vitreous humor of the rabbit eye gave the following values: total vitreous humor, 25.3 (S. D. 1.8) mM/liter; ciliary body area, 31.3 (S. D., 3.5) mM/liter; central core, the area from the posterior capsule of the lens to within 2 to 3 mm. of the posterior pole of the vitreous humor, 24.8 (S. D. 2.1) mM/liter, and the peripheral ring, 23.9 (S. D., 1.9) mM/liter. In an additional number of experiments the core and periphery section were analyzed as one section ("rest") and gave a value of 24.0 (S. D., 2.6) mM/liter.

The total volume of the vitreous humor of rabbits weighing between 4 and 6 lb. was estimated to be 1.47 ml. (S. D. 0.22 ml.); that of the ciliary body area was 0.54 ml. (S. D. 0.17 ml.).

Addendum

Shortly after this article was submitted for publication a preliminary note by Davson and Luck (*J. Physiol.* 130:48P, 1955) was brought to our attention by Dr. John E. Harris, in which the authors reported that the bicarbonate ion concentration in the vitreous humor was 97% of that in the aqueous humor of the anterior chamber of the rabbit eye. They also observed that the concentration in the anterior segment of the vitreous humor was greater by some 18% than in the posterior segment, indicating the effects of influx of bicarbonate ion from the aqueous humor.

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Cytomegalic Inclusion Disease

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Cytomegalic inclusion disease is a multisystem virus disease which is typified pathologically by an inclusion-containing giant cell that appears predominantly in epithelial linings of visceral and cerebral epithelium. It occurs most commonly in the newborn but may involve any age group and generally runs a fatal course. Until recently it has been recognized only at autopsy. Descriptions of this disorder date back as far as 1904, but not until recent years has it evolved as a disease entity of clinical importance.*

In infants its time of onset is somewhat variable, which suggests that it may be contracted either in utero or postnatally. Wyatt and co-workers, in summarizing 66 cases, reported 5 in stillborn babies, 10 in newborns, and the majority of the remainder in infants under 12 months of age.[3]

Since this is a multisystem disease in which no one system is always involved, the clinical characteristics are somewhat poorly defined, but usually it appears as an acute or subacute febrile illness. Other common manifestations are prematurity, jaundice, bleeding tendency, progressive pneumonia, nephrosis, splenomegaly, hepatomegaly, and neurological disturbances. Clinically it has been oftenest confused with hemolytic disease of the newborn, congenital syphilis, and toxoplasmosis. The vital structures most commonly involved are liver, lungs, kidneys, thyroid gland, pancreas, brain, pituitary gland, and spleen.† In the few questionable cases reported in adults, the disease is characterized by progressive severe pneumonitis.‡

The cause is presumably a virus related to the virus of salivary gland disease that occurs in laboratory animals. The virus is species specific, and efforts so far to isolate the human strain or transmit human inclusion disease to experimental animals have failed.[7] The etiology and its relation to inclusion disease of laboratory animals are suggested by the presence in both diseases of a characteristic giant cell that gives origin to the name.[8] These are large mononuclear cells, usually epithelial in origin, measuring from 20μ to 35μ in diameter and containing both intranuclear and cytoplasmic inclusions. In the fully developed cell the nuclei are oval, measuring 10μ to 15μ in diameter, and are eccentrically placed. The nuclear inclusion lies centrally and stains deeply. It is often separated from the nuclear membrane by a clear zone, and the remaining nuclear material forms a thin rim about the periphery. The cytoplasmic inclusions are smaller and less distinct. They usually assume a crescentic pattern and have a powdery appearance.[7]

The virus has a predilection for epithelial cells but may also appear in endothelium.[9] It is oftenest found in cells lining the ducts of various organs, alveoli of lungs, and tubular epithelium of the kidney. In the tissues these inclusion-

Submitted for publication June 18, 1956.

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* References 1 and 2.

† References 3 and 4.

‡ References 5 and 6.

bearing cells are often accompanied by an infiltration of lymphocytes, macrophages, and reactive fibrosis. This produces cirrhosis in the liver, and interstitial pneumonitis of the lungs and may produce obstruction of the kidney tubules. In the kidney the cells slough into the urinary tract and may be demonstrated in the urine, making clinical diagnosis possible.§

When the brain is involved there is gross softening with focal necrosis and mononuclear infiltration. Radiologically demonstrable calcium deposits also occur. The appearance and distribution of this calcium differs from toxoplasmosis, with which this disease has been confused. In cytomegalic inclusion disease the calcium is prone to deposit in the walls of the lateral ventricles, including the body and lateral horns. These deposits are more diffuse and form an indistinct linear pattern, in contrast to the usual shotty disseminated deposits in toxoplasmosis[9] (Figs. 1 and 2).

Cytomegalic inclusion disease is of particular interest to the ophthalmologist because of confusion with toxoplasmosis. Although no distinctive type of chorioretinal lesions have been reported, nondescript retinal infiltrates have been observed in the fundi of one reported case. Histologically these consisted of lymphocytic and histiocytic infiltration with glial proliferation in the ganglion-cell layer. Vasodilatation and thickening of the ganglion-cell layer were also noted. Adjacent areas showed loss of ganglion cells and light infiltration of lymphocytes and histiocytes.[4] In most instances, however, examination of the fundi has not been made either clinically or pathologically. It is the purpose of this report to present a case of cytomegalic inclusion disease demonstrating the usual visceral and cranial involvement and inclusion-bearing cells in the choroidal and retinal vasculature.

§ References 4 and 10.

Fig. 1.—Cytomegalic inclusion disease. The calcium deposits are diffuse and outline the lateral ventricles of the brain.

Fig. 2.—Toxoplasmosis. Calcium deposits are discrete and disseminated.

Report of a Case ||

A white premature female infant was born at Multnomah County Hospital, after 38 weeks gestation, on June 1, 1955. Birth weight was 2200 gm. The mother, a primipara, had been previously admitted on March 16, 1955, at approximately 27 weeks gestation, because of pneumonia. She was treated with antibiotics and subsequently discharged on March 20, 1955. There was no history of virus infection in the first trimester of pregnancy, nor was any vaginal bleeding noted during the entire pregnancy. Bronchiectasis had been detected in 1954 at the age of 17 years. The mother's blood type was Group A, Rh-positive, and serologic tests were negative. The incidence of familial anemia was not known.

The infant was seen shortly after birth, at which time she appeared acutely ill, having generalized petechiae and shallow, rapid respirations. She had very poor muscle tone. Icterus was marked. Liver was palpable 4 cm. below the right costal margin, and the spleen was 5 to 6 cm. below the left costal margin. Auscultation of the chest showed poor aeration and many rales bilaterally.

Hemoglobin was 11.2 gm., and red blood cell count was 4,200,000. White blood cell count was 26,300, with 27% polymorphonuclear cells, 1% eosinophiles, 70% lymphocytes, and 2% monocytes. There were 67 nucleated red cells per 100 white blood cells. The reticulocyte count was 4.8%. The infant's blood type was Group AB, Rh-negative. The Coombs test was negative. Van den Bergh test was as follows: total bilirubin, 18.4 mg.; direct-reacting, 11.4 mg., and indirect-reacting, 7 mg. per 100 cc. Red cell fragility began at 0.44% sodium chloride and was complete at 0.28% sodium chloride. Examination of a single scanty urine sample for inclusion-bearing cells was negative. A blood culture was taken, and no organisms were found. Sputum from the mother was negative for acid-fast bacilli and inclusion-bearing cells. The mother's platelet count was 133,000.

X-ray of the skull showed numerous small calcifications appearing to lie in a linear arc along the dorsum of the lateral ventricles (Fig. 1).

|| The clinical features establishing a definitive premortem diagnosis in this and another case will be submitted for separate publication by the Department of Pediatrics of the University of Oregon Medical School.

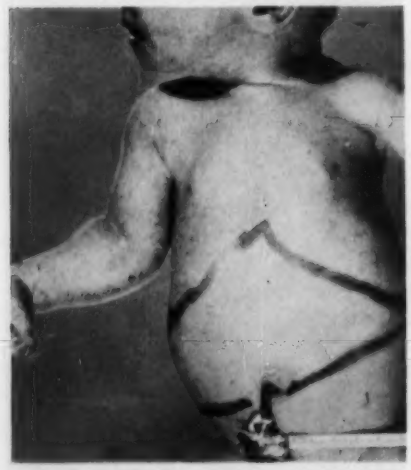

Figure 3

Figure 4

The infant became progressively more lethargic and began coughing up blood on June 2, 1955. She died at 12:05 p.m. June 2, 1955, at the age of approximately 33 hours.

Gross Description.—Gross examination revealed an unembalmed body of a white girl whose general development and state of nutrition appeared to be that of a small newborn infant which weighed 2200 gm. The skin was a bright deep yellow and contained innumerable petechiæ over the entire body surface (Figs. 3 and 4). The chest was symmetrical, and the abdomen was slightly rounded. The upper extremities were normal except for a bluish-purple discoloration beneath the fingernails. The lower extremities were unchanged except for a right talipes varus and discoloration of toenails similar to that of the fingernails.

Primary Incision: When the abdomen and chest were opened the viscera were found to be lying in their usual positions and in normal relations to one another. The liver and spleen were obviously enlarged, and multiple small petechial hemorrhages covered the peritoneum. The lungs were lying free within the pleural spaces, without adhesions or evidence of inflammation. The thymus was grossly

Fig. 5.—Note enlarged liver and spleen and serosal hemorrhages.

normal for a newborn infant. The pericardium was smooth in its entirety; however, it was the site of petechial hemorrhages on both the external and the internal surfaces. Both visceral and parietal pleurae likewise contained petechial hemorrhages (Fig. 5).

Lungs: Both lungs together weighed 60 gm. and were relatively normal in size but were somewhat firmer and wetter than usual. The cut surface of the lungs presented a finely lobulated pink to red appearance and contained little air. Much blood was easily expressd from the surfaces, but there was no evidence of inflammatory reaction.

Heart: The heart weighed 26 gm. All chambers were normal in size and relation to one another. The epicardium was smooth throughout but contained innumerable small petechial hemorrhages. A few petechial hemorrhages were scattered through the myocardium.

Spleen: The spleen weighed 45 gm. and was of firmer consistency than normal. The cut surface had a fairly homogeneous bright red granular appearance. The capsule was smooth, and the contour was normal.

Liver: The liver weighed 100 gm. and was of the usual contour but definitely enlarged with rounded edges. It was deep olive-green and had a leathery consistency. The usual lobular architecture was lacking. The gall bladder was in the usual position and contained approximately 2 cc. of white mucoid material. The ducts were patent throughout, and there were no anomalies.

Pancreas and Adrenal Gland: These showed no gross abnormalities.

Gastrointestinal Tract: Except for serosal petechiae the intestines, stomach, and esophagus showed no gross abnormality.

Genitourinary Tract: The left kidney weighed 18 gm., and the right kidney, 16 gm. The capsules stripped with ease, revealing a smooth subcapsular surface. The cut surface of the kidney showed cortical and medullary markings. However, the blood vessels within both kidneys were congested. The calyceal systems were unchanged, as were the ureters, urinary bladder, and urethra.

Head: On opening, no changes were noted about the dura over the vertex of the brain. Many petechial hemorrhages were noted in the leptomeninges. The slightly dilated ventricles contained bloody cerebral-spinal fluid. The lateral walls of both lateral ventrices were yellow-white. There were innumerable petechiae within the walls of the ventricles, and in the right ventricle there was approximately 5 cc. of clotted blood. The convolutions and gyri of the brain were grossly normal. The right hemisphere of the cerebellum was most severely involved with hemorrhage and necrosis.

Microscopic Findings.—Liver: Sections showed a remarkably thickened capsule made up of fibrous tissue with subcapsular scarring extending into the liver parenchyma. Accompanying the subcapsular strands of fibrous tissue were many lymphocytes. In the portal areas throughout were dense collections of lymphocytes and nucleated red cells. In the biliary ducts of the portal system there were many swollen epithelial cells two to three times normal size. Large inclusion bodies, staining dark homogeneous purple, were in the nuclei. These large inclusion-containing cells were of sufficient size to obstruct the biliary ducts. The liver cells were reduced in number and were uniformly filled with yellow pigment. The connective tissue stroma between the liver-cell cords was diffusely increased throughout, and fibrous tissue was increased in the portal areas and extended

almost completely around the distinguishable liver lobules. The central veins were unchanged. Scattered collections of immature leucocytes and erythrocytes were present in the portal areas.

Kidney: The capsule was unchanged. In the subcapsular region there were many dense collections of lymphocytes and nucleated red and white cells. Lining the proximal convoluted tubules were multitudes of large swollen cells with deep homogeneous-purple-staining nuclear inclusions. These cells in some areas occluded the lumen of the tubule. Some of the cells contained cytoplasmic inclusions as well. A few inclusion-containing cells were free within the lumen of the collecting tubules, and many of the intact tubules were filled with yellow casts. The glomeruli were unaltered; however, there was hemorrhage and necrosis of the kidney parenchyma most marked at the junction between the cortex and the medulla. Focal areas of extramedullary hemopoiesis were present in the cortex.

Pancreas: The pancreas showed, for the most part, a normal architecture with minimal increased intralobular fibrous tissue. Large cytomegalic inclusion bodies containing both intranuclear and cytoplasmic inclusions were present within an occasional duct and islet.

Salivary Glands: The submaxillary and parotid glands showed typical cytomegalic inclusion-containing cells within the ducts. They were present in both the large and small ducts and partially obstructed the smaller ones.

Thyroid: Sections showed many areas containing swollen follicular epithelial cells with the characteristic large intranuclear inclusion bodies (Fig. 6).

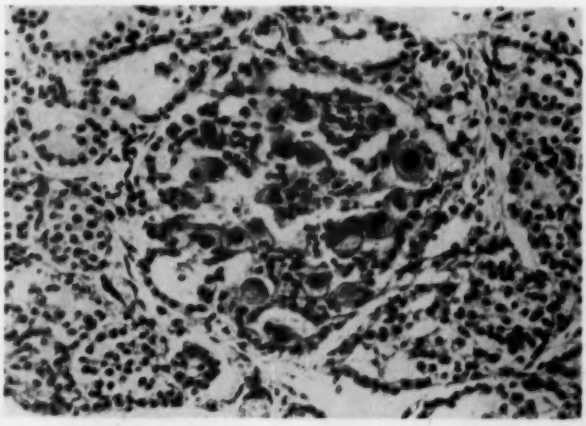

Fig. 6.—Thyroid. Note large classical inclusion-bearing cells.

Spleen: Sections demonstrated only red pulp. The white pulp was obliterated, with only a few lymphocytes present. There was an extreme extramedullary hemopoiesis, as evidenced by a large collection of immature white cells and nucleated red cells.

Central Nervous System: Multiple sections were taken through the brain. The process noted grossly along the lateral ventricles proved to be amorphous collections of calcium underneath the ventricular walls. In these regions there was necrosis of the brain substances surrounding the calcium. Sections through the cerebellum showed extreme necrosis, but no inclusion-bearing cells were identified. The ependyma and choroid showed no cytomegalic inclusion-bearing cells.

Lungs: Multiple sections were taken through the lungs. All showed essentially an extreme edema and very little air-filled lung parenchyma. There was extravasation of blood everywhere. Within the alveolar spaces were many pigment-filled macrophages. Large cells were present within the lumens of a few of the alveoli, and these contained the typical cytoplasmic and intranuclear inclusions. Rarely an alveolar epithelial cell was found to be enlarged and containing the characteristic cytoplasmic and nuclear inclusions. There was no evidence of swelling of the bronchiolar epithelial cells or the peribronchial glandular epithelium.

Anatomic Diagnosis

1. Cytomegalic inclusion disease
   - A. Generalized petechiae involving skin, all serous surfaces, and arachnoid, with subarachnoid hemorrhages and bleeding into lateral ventricles of brain and subtentorial hemorrhages (approximately 10 ml.)
   - B. Calcifying plaques in walls of lateral ventricles of brain, cortical immaturity, cerebellar necrosis
   - C. Cytomegalic inclusions in renal tubular epithelium, bile duct epithelium, pancreatic duct epithelium and islet cells, salivary duct epithelium, and thyroid follicular epithelium
   - D. Extramedullary hemopoiesis in liver, spleen, and kidneys, with hepatomegaly and splenomegaly
   - E. Portal cirrhosis of liver with severe jaundice
     1. Deformity of right ankle with inversion of plantar surface
     2. Pulmonary edema, hemorrhage, and bronchopneumonia.

Ocular Pathology.—Gross Description: The specimen was a firm, regularly shaped right eye measuring 16×15×15 mm. There was a diffuse corneal haze, which obscured the anterior chamber. However, the chamber appeared shallow, and by transillumination the pupil was regular and measured 6 mm. There was a bluish tinge to the sclera and a slight pigmentation around the inferior temporal limbus.

Inferior horizontal calotte: On opening there was minimal escape of well-formed vitreous. A dark pigmentation was uniformly distributed in the retinal periphery. This had the appearance of pigment or hemorrhage. The retina appeared somewhat contracted but was generally in situ. The nerve head and

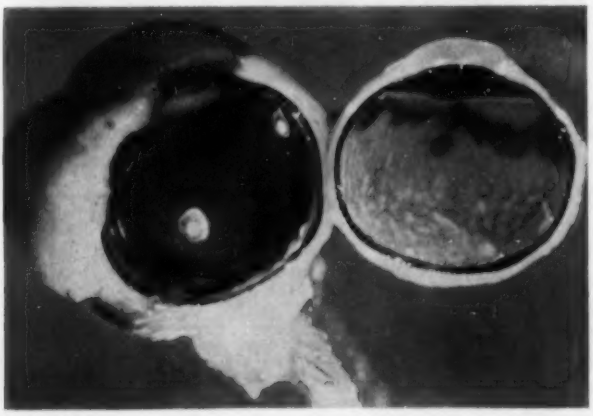

Fig. 7.—Section through gross specimen. Note peripheral retinal hemorrhage.

anterior chamber were not visible from the cut surface. The lens was in situ and appeared somewhat swollen in its anteroposterior diameter. It was densely opaque (Fig. 7).

Microscopic Description: Microscopic sections of this baby's eye showed a well-developed globe with cataractous changes in the lens, partial loss of the anterior chamber, peripheral retinal hemorrhages, endothelial budding in the retina, and scattered inclusion-containing mononuclear cells in the retinal and choroidal vasculature.

Cornea. The cornea was regular in contour and thickness except for a slight corrugation of the anterior surface. There were several dehiscences and folds in the endothelium, which may have been artefacts.

Anterior chamber and chamber angle. The anterior chamber was partially obliterated because of anterior peripheral synechiae. Centrally there was deposition of pink-staining protein-rich fluid. The chamber angles were closed, and the trabecular meshwork and Schlemm's canal were compressed.

Lens. The lens was in situ and showed extensive corrugation of its capsule. The anterior surface was depressed centrally. The subcapsular cortex showed numerous areas of liquefaction indicative of cataractous change.

Uveal tract. The pigment epithelium of the iris was fragmented in the pupillary area. The iris stroma showed the dense cellularity usual for this age group. There was an unusual degree of stromal vascularization, and a number of the vessels contained nucleated red cells. The ciliary body was well formed, as well as the processes. The choroid was well vascularized, and, in most of the sections studied, large mononuclear cells varying in size up to 35μ were found within the lumina of some of the larger vessels (Fig. 8). These abnormal cells contained cytoplasmic and intranuclear inclusions.

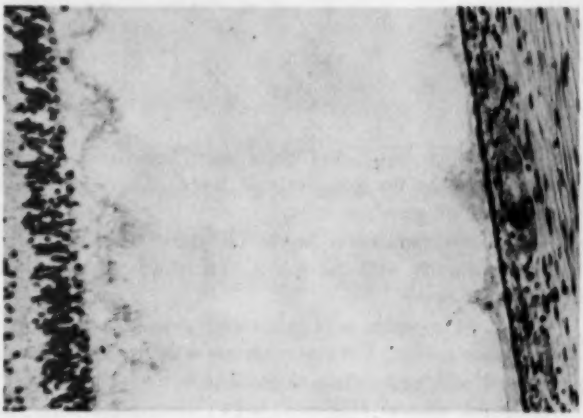

Fig. 8.—Inclusion-bearing cell in choroidal vessel.

Retina. The retina presented a moderate degree of autolysis. A most striking feature was an extensive endothelial budding in the ganglion-cell layer at the periphery (Fig. 9). Many of these buds were canalized, and others were occluded. Within the canalized channels nucleated red cells and extruded fragments of nuclei were present in high concentration. An occasional cytomegalic giant cell was evident (Fig. 10). Disseminated areas of gliosis were present in

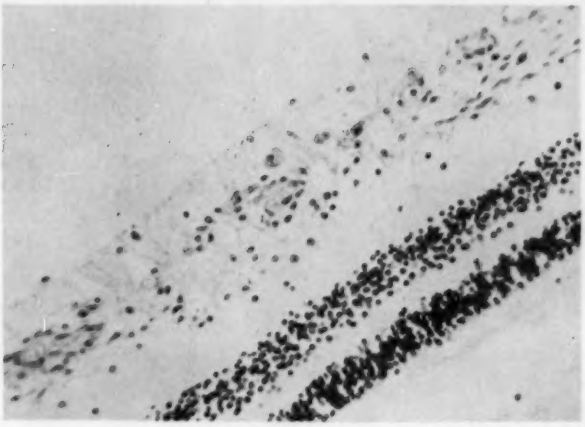

Fig. 9.—Section through retina demonstrating neovascularization and endothelial budding in ganglion-cell layer.

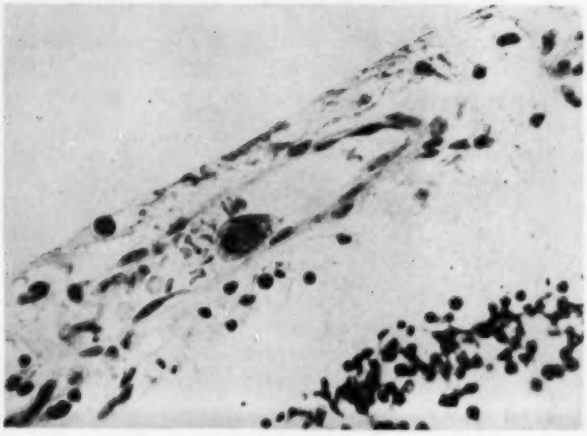

Fig. 10. — Inclusion-bearing cell in retinal vessel.

the nerve fiber layer, and there were extensive peripheral hemorrhages which predominated in the ganglion-cell layer. There was an appreciable reduction in the number of ganglion cells.

Optic nerve and nerve head. The nerve head was flat, and the cribriform plate was in continuity with the sclera. There was no myelinization of the nerve fibers in the optic nerve.

Sclera. The sclera was intact and showed nothing of note.

Vitreous cavity. Formed vitreous was present anteriorly, and this was lightly permeated with red cells and fibroblasts.

Anatomic Ocular Diagnosis.—(1) systemic disease: cytomegalic inclusion disease: (2) lens: cataract; (3) retina: autolysis, hemorrhage, gliosis, neovascularization.

Comment.—The most significant findings in this one eye removed at autopsy consisted of extensive endothelial proliferation, peripheral retinal hemorrhages, cataract, and malformation of the anterior chamber. Histologically the retinal alterations were limited, for the most part, to the ganglion-cell and nerve fiber layer. The genesis of the extensive endothelial budding and hemorrhage within the

nerve fiber layer is not apparent. In all probability this tissue reaction is not peculiar to the eye but rather is of the same derivation as the petechial hemorrhages in the skin and viscera and probably reflects severe liver damage or depression of bone marrow activity. Considering the retinal alterations, surprisingly few inclusion-bearing cells were found in the retina and these were confined to the vessels. No inclusion-bearing cells were found in the tissue spaces or epithelium of pars plana. In contrast to the situation in toxoplasmosis, there was no appreciable inflammatory reaction in the sections studied and the presence of few phagocytic cells was accounted for by hemorrhage. In the choroid the only appreciable abnormality was the incidence of inclusion-bearing cells in the lumina of vessels. The origin of these cells is obscure, but their presence is most easily explained by virus invasion of endothelium. Again, there was no appreciable inflammatory reaction. The cataract and malformation of the anterior chamber are difficult to evaluate, since there have been no previous reports to indicate that this is a common complication. However, if this is a concomitant of this disease then congenital anomalies such as those associated with measles in the first trimester of gestation must be included in the differential diagnosis.

It appears from this and one other report that the retinopathy of cytomegalic inclusion disease is nondescript and may be of little diagnostic value. However, this can be determined only by further observations.

Summary

Cytomegalic inclusion disease is a disease entity of increasing importance. In the past it has been oftenest confused with hemolytic disease of the newborn, syphilis, and toxoplasmosis. From the viewpoint of the ophthalmologist, the clinical findings simulate toxoplasmosis and possibly measles in the first trimester. These include retinopathy, intracranial calcifications, and cataract. The features that distinguish this disease and differentiate it from toxoplasmosis are discussed and illustrated with a case report.

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Novobiocin, A New Antibiotic

Ocular Penetration and Tolerance

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With the technical assistance of Marie Ronca

Introduction

Novobiocin is the generic name that has been adopted for two new antibiotics which were discovered independently of each other and later found to be identical. One of these, Cathomycin,* is derived from Streptomyces spheroides n. sp.,[1] and the other, streptonivicin,† is derived from Streptomyces niveus n. sp.[2] Early studies of the antibacterial activity of these antibiotics[3] indicated a very close similarity in their activity, which led Welch and Wright[4] to undertake a study of their physical properties. Close similarities of the ultraviolet and infrared absorption spectra and other physical properties of these two antibiotics showed that they were identical. Included in this work was a third antibiotic, Cardelmycin ‡ (crystallinic acid; formerly referred to as PA 93), which was also found to be identical to streptonivicin and Cathomycin. With the wide variety of names attending the independent discoveries of this antibiotic, some confusion is bound to occur. Another new antibiotic, "Albomycin," discovered in the Soviet Union and derived from Actinomyces subtropicus, is apparently not identical to novobiocin[5] and must not be confused with Albamycin, which is one of the current trade names for novobiocin.

Novobiocin is a dibasic acid which is available as a monosodium crystalline salt. The monosodium form is soluble in water and in slightly alkaline solutions but is insoluble in acidified solutions. The color is white with a slightly yellowish tinge. The compound has been shown to be a single structure and to consist of carbon, oxygen, hydrogen, and nitrogen.§

Novobiocin has been shown to be active against a number of Gram-positive and certain Gram-negative micro-organisms. Among those bacteria reported to be most sensitive to novobiocin in vitro are Staphylococcus aureus, Diplococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, and Corynebacterium diphtheriae; other micro-organisms reported to be fairly sensitive to the drug include Streptococcus faecalis, viridans Streptococcus, Bacillus anthracis,

Received for publication June 8, 1956.

From the Research Department of the Wills Eye Hospital. Research Fellow in Ophthalmology (Dr. Paul).

This investigation was supported in part by a research grant (2B-5076C) from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, Public Health Service.

* Cathomycin is the trade name of Sharp & Dohme, Division of Merck & Co., Inc., for novobiocin.

† Streptonivicin, originally the generic name of novobiocin, is a product of The Upjohn Company, which now uses the trade name of Albamycin.

‡ Cardelmycin is the trade name of Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc., for novobiocin.

§ References 6 and 7.

Neisseria, Pasteurella multocida, Erysipelothrix, Proteus vulgaris, and Salmonella typhosa.|| Some of the latter group show sensitivity only with regard to certain strains of the species concerned.¶ Prominent among the few Gram-negative bacteria that show sensitivity to novobiocin are certain strains of P. vulgaris.#

Good results have been obtained with the use of novobiocin in vivo in patients. The drug has been effective particularly against S. aureus,* pyogenes,† B. anthracis,[19] and D. pneumoniae.[20] One of the promising features of this new antibiotic is that it shows no cross resistance with other antibiotics.‡ In a series of 48 strains of S. aureus, isolated from suppurative lesions in patients, all were found to be sensitive to less than 0.4γ/ml. of novobiocin.[13] Many of these strains were, nevertheless, resistant to more than 50γ/ml. of streptomycin, penicillin, and tetracycline and to more than 25γ and 18γ/ml. of erythromycin and chloramphenicol, respectively. Development of resistance to novobiocin in previously sensitive strains of bacteria has been reported.§

In humans the drug has been shown to be well tolerated when administered intramuscularly, intravenously, and orally.|| There has, however, been a small percentage of cases with fever and dermatologic reactions. Usually, these reactions disappear on stopping the drug. Chronic toxicity studies on rats and dogs have demonstrated disturbances in the hepatic and hematologic systems due to novobiocin.[21]

Oral administration rapidly leads to high serum levels of the drug ¶ which last several hours. The drug subsequently may be detected in the pleural and ascitic fluids, bile, urine, and feces. Novobiocin has not been detected in the cerebrospinal fluid of patients treated with it.# The drug appears to be reversibly bound by serum protein and has been shown to be inactive in this state.*

The purpose of the present study is to determine whether or not this new antibiotic can penetrate into the chambers of the eye of experimental animals and how well it can be tolerated by ocular tissues.

Methods

In order to facilitate detailed study of the intraocular penetration and tolerance to novobiocin, the following modes of administration were employed: (*a*) topical application to normal unabraded and mechanically abraded corneas; (*b*) iontophoresis on normal unabraded corneas; (*c*) Subconjunctival injections; (*d*) intramuscular administration; (*e*) intravenous administration to animals with normal and chemically inflamed eyes; (*f*) intracameral injections into the aqueous and vitreous humor.

Rabbits of average weight (2.5 kg.) were used in all experiments. After local application of the drug and prior to every ocular manipulation the eye was washed

|| References 1, 3, 8-15, and 20.
¶ References 3, 13, and 15.
# References 13 and 15.
* References 16-19.
† References 16 and 19.
‡ References 10-13 and 19.
§ References 10, 11, and 19.
|| References 13, 15-20, and 22-24.
¶ References 10, 11, 13, 15, 19, 20, and 22.
#References 10, 11, 13, 15, 19, and 22.
* References 10, 11, 13, and 15.

with sterile saline for one minute and sterile tetracaine (Pontocaine) (0.5%) was instilled into the lower conjunctival cul de sac. Aqueous and vitreous were aspirated by use of a tuberculin syringe (wetted with 1:100 heparin) fitted with a 27- and a 21-gauge needle, respectively. For topical application, 8 drops (about 0.5 cc.) of novobiocin solution were instilled every 10 minutes into the lower conjunctival cul de sac for 30 minutes. Fresh solutions of crystalline novobiocin sodium were prepared daily by dissolving the drug, taken from capsules,† in sterile distilled water and using it directly.

Ocular fluids and serum were assayed for novobiocin by the serial dilution technique. Brain-heart infusion broth was employed throughout in 2 ml. amounts in culture tubes. This volume permitted a lower initial dilution of the ocular fluids, which were generally obtained in small (0.2 ml.) amounts. Threefold dilutions were made starting at 1:10 and carried through 1:2430. The first dilution, however, according to the procedure followed, was always changed to 1:20 by the addition of 1 ml. of extra broth in order to restore its volume to 2 ml. A strain of S. aureus,‡ highly sensitive to novobiocin, was employed in the bioassay procedure. Each day a young (6- to 18-hour) broth culture was diluted in broth to give an optical density in the range of 65 to 75 units on the Klett-Summerson photoelectric colorimeter with use of the broth as blank and a No. 54 green filter. A 0.1 ml. amount of this suspension served as inoculum for each broth mixture and was shown to contain roughly 2×10^6 viable organisms by the pour plate technique. In this study it was found that growth inhibition after 48 hours was generally permanent; therefore this reading was adopted for evaluating all tests. Twenty-four hour results were referred to only in doubtful cases. Daily employment of novobiocin broth controls with use of twofold dilutions yielded an average end-point of 1γ/ml. as the sensitivity of the test organism § utilized. This figure served as the standard for estimating approximate novobiocin levels in the test fluids. Gram stains were made on 10% to 20% of all cultures as a check against contaminations.

Results

Topical Application to Normal Unabraded Corneas.—Novobiocin in solutions of 10,000γ; 25,000γ; 50,000γ, and 100,000γ/ml. was employed. Aspiration of aqueous humor was done at one-quarter-, one-half-, one-, two-, and three-hour periods. Novobiocin could not be detected in the aqueous after administering 10,000γ/ml. but was detectable in low concentration (less than 30γ/ml.) three hours after administration of 25,000γ, 50,000γ, and 100,000γ/ml. (Table 1).

Topical Applications to Mechanically Abraded Corneas.—It was found that novobiocin, when administered in the strength of 10,000γ/ml., showed penetration into the aqueous humor after one hour and was still detectable in the aqueous up to a period of five hours. The peak concentration demonstrated was 20γ to 30γ/ml. The antibiotic could not be detected in the aqueous for longer than six

† The antibiotic was supplied in capsular form as Cathomycin sodium, Lot No. P. D. 1163-301C, by Sharp & Dohme, Division of Merck & Co., Inc. Each capsule was reported to comprise crystalline novobiocin sodium, 250 mg., and magnesium stearate, 1 mg.

‡ Strain No. 10 from our own collection.

§ Strain No. 10 was later compared with Micrococcus pyogenes var. aureus, A. T. C. C. Strain 9144 (N. G. Heatley strain Oxford H. assay of penicillin) and found to be equal in sensitivity to novobiocin by the above method.

TABLE 1.—*Penetration of Novobiocin into the Aqueous Humor of Rabbit Eyes* After Local Administration of 10,000 γ/Ml.*

Interval Between Administration of Drug and Withdrawal of Aqueous, Hr.	Concentration of Novobiocin Found in Aqueous, γ/Ml.	
	Normal Cornea	Abraded Cornea
¼ and ½	0	0
1	--	20
1½	--	20-30
2	0	20-30
2½	--	20
3	0†	20
4	--	<20
5	--	<20‡

* Each determination represents an average of tests on five eyes.
† 25,000 γ; 50,000 γ, and 100,000 γ/ml. applied to normal corneas showed penetration less than 30 γ/ml. in three hours.
‡ Novobiocin was not found in the aqueous 6 and 24 hours after administration of solutions of 50,000 γ; 100,000 γ, and 500,000 γ/ml.

hours after administration, although strengths greater than 50,000γ/ml. were employed (Table 1).

Iontophoresis.—Novobiocin in 12,500γ and 25,000γ/ml. concentrations was employed on eight eyes. A 2.0 ma. current was used, and iontophoresis was carried out for 15 minutes in each case. In this series of experiments the bioassay of the aqueous humor failed to show any penetration of the drug.

Subconjunctival Injections of Novobiocin in Normal Eyes.—Administration of 3000γ and 6000γ of antibiotic showed no detectable penetration into the aqueous. Larger doses, of 12,500γ and 50,000γ/ml., resulted in penetration of the aqueous detectable up to a period of five hours. Injecting doses of 100,000γ and 500,000γ resulted in a penetration of the vitreous as well as of the aqueous; in the vitreous the antibiotic could still be detected after 6 hours but not after 24 hours, while in the aqueous it was detectable after 24 hours (Table 2).

TABLE 2.—*Penetration of Novobiocin into Aqueous Humor of Normal Rabbit Eyes* After Subconjunctival Injection*

Amount of Novobiocin Injected, γ	Interval Between Administration of Drug and Withdrawal of Ocular Fluid, Hr.	Concentration of Novobiocin Found, γ/Ml.	
		Aqueous	Vitreous
3,000	2	0	
6,000	2	0	
12,500	½	0	
	2	30-90	
	3	<20	
	4½	<20	
	5	<20	
25,000	2	90	
50,000	2	90-270	
	3	90-270	
100,000	6	90-270	30
	24	30-90	0
500,000	6	>2,430	<20
	24	270	0

* Each determination at 100,000 γ and 500,000 γ represents tests on one eye each; all others represent an average of tests on five eyes each.

TABLE 3.—*Penetration of Novobiocin into Aqueous Humor of Normal Rabbit Eyes* After Intramuscular Injection*

Amount of Novobiocin Injected, γ	Interval Between Administration of Drug and Withdrawal of Ocular Fluid and Serum, Hr.	Concentration of Novobiocin Found, γ/Ml.	
		Aqueous and Vitreous	Serum
100,000	2-24†	0	0
1,000,000	3-4	0	<240
	6	0	80
	24	0	0

* Each determination represents an average of tests on two eyes.
† The aqueous was tapped in different animals at 2, 3, 4, 5, 7, and 24 hours.

Intramuscular Administration.—Novobiocin when given in 100,000γ to 1,000,000γ doses was not detected in the chambers of the eye. The antibiotic was found only in the blood after administration of 1,000,000γ (Table 3).

Intravenous Administration to Rabbits with Normal Eyes.—Novobiocin given intravenously in doses up to 100,000γ could not be detected in the anterior chamber of the eye. When given in doses of 500,000γ it could be detected in the aqueous humor from one to three hours after administration. After four hours the antibiotic was not detected in the aqueous, although it could still be demonstrated in the blood. Novobiocin was not demonstrated in the vitreous in all of these tests. One million micrograms proved to be lethal to an average-weight rabbit (Table 4).

Intravenous Administration to Rabbits with Chemically Inflamed Eyes.—Novobiocin, when given in doses of 100,000γ, could be detected in the primary aqueous within one to one and one-half hours after administration in quantities less than 30γ/ml.; it was also demonstrated in the secondary aqueous in concentrations varying from 20γ to less than 90γ/ml. Within two hours after administration it could not be detected in either type of aqueous. The antibiotic, when given at doses of 400,000γ to 500,000γ, was detected in the primary aqueous at 30γ to 90γ/ml. and in the secondary aqueous at 90γ to 810γ/ml. This penetration of the antibiotic was found to persist up to three hours after administration (Table 5).

TABLE 4.—*Penetration of Novobiocin into Aqueous Humor of Normal Rabbit Eyes* After Intravenous Injection*

Amount of Novobiocin Injected, γ	Interval Between Administration of Drug and Withdrawal of Ocular Fluid and Serum, Hr.	Concentration of Novobiocin Found, γ/Ml.		
		Aqueous	Vitreous	Serum
20,000	½-4†	0	0	0
100,000	½,1	0	0	27-81‡
	2, 3, 4, 5	0	0	0§
500,000	1	<30	0	>240
	2	20-30	0	>240
	3	<30	0	80-240
	4	0	0	27

* Each determination represents an average of tests on two eyes.
† The aqueous was tapped in different animals at one-half, one, two, three, and four hours.
‡ Only the one-hour serum was tested.
§ The two-hour serum was doubtful and may have had less than 20 γ/ml.

TABLE 5.—*Penetration of Novobiocin into Aqueous Humor of Rabbit Eyes* That Received Acid Burns of the Cornea Followed by Intravenous Injection of Novobiocin*

Amount of Novobiocin Injected, γ	Interval Between Administration of Drug and Withdrawal of Ocular Fluid, Hr.	Concentration of Novobiocin Found, γ/Ml.	
		Primary Aqueous	Secondary Aqueous†
100,000	1-1.5	0-<30	30-<90
	2	0	0
400,000	1	30-90	90-180
500,000	3	30-90	270-810

* Each determination represents an average of tests on two eyes.
† Secondary aqueous was obtained one-half to three-quarters of an hour after the primary aqueous.

Intra-Aqueous and Intravitreal Injections.—Novobiocin in doses of 1000γ (0.05 ml.) and 25,000γ (0.125 ml.) was injected into the aqueous and vitreous. After administration of 1000γ of antibiotic into either the aqueous or vitreous it could not be detected in the other fluid after 3, 4, 5, or 24 hours. With intra-aqueous injections the drug could be detected only after three and four hours in that fluid. With intravitreal injections, however, the drug could be detected for as long as 24 hours in that fluid (Table 6). After administration of 25,000γ,

TABLE 6.—*Concentration of Novobiocin Remaining in the Aqueous and Vitreous of Normal Rabbit Eyes After Intra-Aqueous and Intravitreal Injections*

Amount of Novobiocin Injected, γ	Interval Between Administration of Drug and Withdrawal of Ocular Fluid, Hr.	Concentration of Novobiocin Found, γ/Ml.			
		Injection into Aqueous Humor		Injection into Vitreous Humor	
		Aqueous	Vitreous	Aqueous	Vitreous
1,000*	3	<30-90	0	0	270-810
1,000	4	20-30	0	0	90-270
1,000	5	0	0	0	270-810
1,000	24	0	0	0	30-90
25,000†	3	90-270			270-810
25,000	4	90-270			810-2,430
25,000	5	270-810			810-2,430
25,000	24	0			90-810

* Each determination represents an average of tests on four eyes.
† Each determination represents an average of tests on two eyes.

novobiocin was detectable somewhat longer in the aqueous and at higher concentrations; in the vitreous the drug was detectable again up to 24 hours but at higher concentrations than that which was found at the lower dose (Table 6).

Ocular Tolerance to Novobiocin.—Intravenous or intramuscular injections even in very high doses did not have any toxic effects on the eye.

Local application of the drug in concentrations greater than 12,500γ/ml. had noticeable toxic effects on the eye. The animals invariably squeezed their eyes after the drug was administered and seemed very uncomfortable. Administration of a solution of 25,000γ/ml. caused, in one hour, conjunctival congestion, de-

epithelization of the cornea, and fine edema of the anterior stroma of the cornea. Increasing dosages enhanced these features, and after application of a solution containing 100,000γ/ml. the damage to the cornea and the conjunctival injection and discharge were very much in evidence. After 24 hours it was found that the damage to the cornea was very slowly repaired in those eyes that received solutions of 25,000γ/ml. of antibiotic. No toxic effect was noted on the uvea. Novobiocin concentration of 100,000γ/ml. was toxic to the anterior segment of the eye. After 24 hours there was a marked conjunctival discharge and injection, uniform staining of the cornea, and a flare in the anterior chamber. A week later there was a superficial vascularization of the cornea and haziness. The flare in the anterior chamber was still present.

The effect of subconjunctival injections of novobiocin was studied with use of concentrations of 12,500γ; 25,000γ; 100,000γ, and 500,000γ. After administration of 12,500γ the cornea stained, but 24 hours later it looked completely healthy, with no other sign of inflammation. A dose of 25,000γ produced, after two hours, corneal staining and irritation of the eye. Twenty-four hours later chemosis of the conjunctiva, injection, and staining of the cornea was noted. No flare was detectable six days later, but superficial vascularization of the cornea was noticed in the area of injection. The higher doses of novobiocin produced marked toxic effects such as extreme damage to the corneal epithelium, flare in the anterior chamber, anterior synechiae, edema of the posterior stroma of the cornea, and edema of the iris in a shallow chamber.

Doses varying from 10γ to 25,000γ were injected into the anterior chamber to study ocular tolerance and toxicity to the drug internally. The results indicated that up to 2000γ in the anterior chamber was tolerated by the eye. These animals were observed for one week and did not show any abnormality. Higher dosages, e. g., 25,000γ, resulted, 24 hours later, in marked conjunctival discharge, chemosis of the conjunctiva, hazy cornea, and deposition of white material in the anterior chamber. One week later the eye was still inflamed and the cornea was almost opaque. The anterior chamber could not be visualized.

Novobiocin doses varying from 10γ to 25,000γ were injected intravitreally, and it was found that up to 1000γ of the drug was tolerated by the eye. Ophthalmoscopy was negative, and no reaction was observed at least one week after these injections. Higher dosages, however, produced opacities in the vitreous, white coating of the retina, edema of the iris, and a fixed dilated pupil. The cornea remained clear.

Ocular Tolerance in Infection.—Experimental infection was produced by injecting approximately 2000 viable cells of S. aureus intracorneally in both eyes of one rabbit. Thirty minutes later 12,500γ of novobiocin was injected subconjunctivally in one eye and the other eye was left as a control. Twenty-four hours later the eye that had received the drug showed marked clearing of the cornea and minimal irritation. The control eye had a corneal ulcer and showed extreme irritation. This procedure was repeated in a second rabbit, but in this case the staphylococci were injected into the anterior chambers. Twenty-four hours later the eye that received the antibiotic showed minimal reaction, a fairly clear cornea, and a fairly clear anterior chamber. The control eye showed a hazy cornea, a shallow anterior chamber, and a 3+ flare with cells.

Comment

From the evidence presented it can be concluded that novobiocin is a useful antibiotic for treating ocular infections, involving sensitive bacteria, in experimental animals. The fact that novobiocin was not tolerated above certain levels in the rabbit eye is an indication that great care as to dosage must be exercised in applying the drug clinically. This study revealed that intravenous novobiocin can lead to low concentrations in the aqueous, especially in rabbits with inflamed eyes. This may be one method of combating sensitive bacteria in intraocular inflammations, but it is partly limited by the large dosage required to effect sufficient blood levels of the drug. Whether or not oral administration in rabbits could lead to similar blood levels is not known, but others || have demonstrated in humans blood levels ranging from 12.8γ to 112γ/ml. during the first six hours following oral administration of 500 mg. of novobiocin. The possibility exists of treating ocular infections in humans by this method, but it is a matter that remains to be settled. The data also pose the further problem of novobiocin penetrability with regard to the posterior segment of the eye. In the rabbit novobiocin did not appear to enter the vitreous by any of the routes used except by subconjunctival injection, and in this instance large, toxic dosages were necessary to effect low vitreal concentrations. After direct intravitreal injections of nontoxic dosages, however, the vitreous maintained high levels of the drug even after 24 hours. According to these findings, when administered locally or subconjunctivally, the drug can be considered to have its greatest effectiveness against external ocular infections and those involving the anterior segment of the eye.

Summary

Novobiocin, a new antibiotic that has a wide range of activity against Gram-positive and some Gram-negative bacteria, was tested for ocular penetrability and tolerance.

Topical application of novobiocin to normal corneas showed no penetration when the concentration applied was 10,000γ/ml. but did show penetration in higher concentrations (25,000γ-100,000γ/ml.), which led to detection of less than 30γ/ml. in the aqueous. Those higher dosages, however, proved to be toxic to the eye. Topical application of 10,000γ/ml. novobiocin solution to mechanically abraded corneas indicated a penetration of 20γ to 30γ/ml. of the drug, which could be detected in the aqueous up to five hours after application. In this strength the drug was very well tolerated by the eye. Higher dosages were found to interfere with reparative processes and were toxic to the eye.

Subconjunctival injections of 12,500γ were very well tolerated by the eyes, and the drug was detectable in concentrations up to 30γ to 90γ/ml. in the anterior chamber. The drug was still detectable in the aqueous up to five hours after administration. Higher doses, like 100,000γ and 500,000γ, were also able to penetrate into the vitreous humor, and the drug was found in the aqueous humor in diminishing amounts up to 24 hours after administration. Dosages above 12,500γ were found to be damaging to the eye.

Intravenous injections of 500,000γ were tolerated by the rabbit, and the drug could be detected in the aqueous humor in concentrations of less than 30γ/ml. Doses below 500,000γ did not lead to detectable amounts in the eye. When the

|| References 13, 15, 19, and 20.

eyes were previously inflamed, lower intravenous doses, like 100,000γ, were able to penetrate into the aqueous humor and could be detected in less than 30γ/ml. concentrations for short periods. On analysis of the secondary aqueous, however, higher concentrations of antibiotic (20γ to 90γ/ml.) were detectable. After administration of 500,000γ of novobiocin intravenously an even greater penetration was detectable in inflamed eyes, the concentration being 30γ to 90γ/ml. in primary and 270γ to 810γ/ml. in secondary aqueous.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

Neuromyelitis Optica with Increased Intracranial Pressure

This case is presented because of the unusual picture of sudden bilateral blindness; the ensuing stormy course, with increased intracranial pressure, and eventual recovery, with optic atrophy as the only residual. The diagnosis of neuromyelitis optica was generally accepted (unanimously by the ophthalmology staff), and since we have found no reported cases with increased intracranial pressure of this magnitude it was thought sufficiently interesting and important to include in the literature.

First Admission

On March 29, 1956, a 13-year-old Mexican girl was admitted to Fresno General Hospital with a complaint of "blindness." Two days prior to admission she had had a sudden onset of severe frontal headaches associated with blurred vision. Within two hours she became totally blind.

Past History.—Approximately one month previously she was diagnosed by the school nurse as having mumps. She was completely well in a few days.

Physical Examination.—The pupils were widely dilated and did not react to light. On convergence, however, they reacted promptly. There was no light perception in either eye. Moderate edema of the disks was present bilaterally. The retinal veins were dilated and tortuous and collapsed with scleral pressure. Pain was elicited on movement of the eyes and by external pressure.

Laboratory Findings.—The WBC count was 24,600/cu. mm., with 71% segmented forms, 25% lymphocytes, 3% stab cells, 1% eosinophils. Urine was normal. Spinal fluid: pressure 190 mm. of water, WBC count 99 cells/cu. mm. (86% lymphocytes, 14% polymorphonuclear cells), sugar 70 mg/100 cc., total protein 30.7 mg/100 cc., colloidal gold curve 0000000000, and culture negative. X-rays of the skull showed no abnormality. Serologic tests and the complement-fixation test for mumps were negative.

Course.—Temperature was 101 F but became normal by the second day. She improved and was discharged on the 17th day, at which time the visual acuity was O. D. 12/400, O. S. 10/400, with return of normal light reflexes. There was minimal evidence of optic disk edema. No other neurological abnormalities were found during hospitalization.

Second Admission

On April 27, 1956, she was readmitted with generalized weakness and muscle pains. Temperature was 100.2 F and remained about 1 degree elevated for the next month. Blood pressure was 160/120. The deep tendon reflexes were hyperactive; abdominal reflexes were normal, and Babinski reflex

Received for publication Aug. 1, 1956.

was negative. There was hyperesthesia of the upper arms and the upper anterior chest wall. Generalized muscle weakness was present, with tenderness to palpation. The optic disk edema had increased slightly. Blood count was within normal limits; the serologic tests were again negative, and the urine was normal and remained so.

During the next few days she complained of increasing pains in the back, legs, arms, and neck. Urinary retention developed, necessitating catheterization for the duration of the illness. Spinal fluid on May 2, 1956: pressure 520 mm. of water, 145 cells/cu. mm. (89% lymphocytes, 11% polymorphonuclear cells), total protein 58.2 mg/100 cc., colloidal gold curve 000111±000; culture on this and other occasions was negative; sugar and chlorides were at the upper limits of normal and remained so for six weeks. Complement-fixation tests for Western equine encephalomyelitis, St. Louis encephalitis, and mumps were negative. On May 4, 1956, there was a sudden change in the vital signs, with a blood pressure of 230/100; pulse rate, 136, and marked papilledema. The patient was very disoriented. Spinal fluid: pressure 510 mm. of water, WBC 288 cells/cu. mm. (96% lymphocytes, 4% polymorphonuclear cells). A blood count revealed that the WBC count had risen to 26,500/cu. mm., with 69% segmented forms, 13% lymphocytes, 8% stab cells, 8% monocytes, 1% eosinophils, 1% basophils. Ventriculography the following day revealed a normal ventricular system and no evidence of a space-occupying lesion. May 7, 1956, the vital signs had improved but the patient remained disoriented. The cerebrospinal fluid pressure continued at a level near 600 mm. of water. On May 11, 1956, there was definite paralysis of isolated muscle groups and a flaccid paralysis of the left lower extremity. Intercostal and diaphragmatic function was poor, and the patient was placed in a respirator but remained confused. The cerebrospinal fluid pressure slowly began to fall, and on May 18, 1956, it was 310 mm. of water and a corresponding decrease of the cells occurred, with lymphocytes continuing to predominate. The blood count also decreased toward a normal level and distribution. By the first of June the patient showed remarkable improvement in sensorium. There was no residual muscle paralysis, and the papilledema had completely disappeared, leaving marked temporal pallor bilaterally. Her visual acuity was recorded at O. D. 20/400, O. S. 20/200. All attempts to record visual fields were unsuccessful. She was discharged on July 2, 1956, with a cerebrospinal fluid pressure of 19 mm. of water.

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Annual Reviews

Lips, Lacrimal Apparatus, and Conjunctiva

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Lids

Blepharophimosis

Blepharophimosis combined with ptosis is one of the most difficult problems with which the ophthalmic plastic surgeon must deal. This congenital condition is seen more frequently and is less successfully treated than the scanty literature would indicate. The operations of 50 years ago are still being used by most surgeons, perhaps with some minor modifications. The results have left much to be desired—and still do. Our best and often-repeated efforts have resulted in some improvement in the appearance of most of these patients, but they are at best far from good. During the period of this review there have been three excellent articles on the care of this condition. Those of us who attempt the surgical care of these patients are indebted to Hughes,[1] Spaeth,[2] and Johnson[4] for their contributions.

Hughes[1] advises a threefold and sometimes fourfold approach to the problem. He elongates the shortened palpebral fissure by a simple lateral canthoplasty, as others have done. He attacks the characteristic widened intercanthal distance by a Y-incision over the canthal area with the single arm toward the bridge of the nose. Preparatory to closing the incision in a V-fashion to obliterate the epicanthal fold, as in Verwey's technique, he creates a canthal depression by excising a moderate amount of tissue overlying the attachment of the medial canthal ligament. He shortens the medial canthal ligament by a traction suture through it, near its bifurcation, carried beneath the periosteum and brought out through the skin over the bridge of the nose, tied over a bolster. Following closure of the Y in a V-fashion good results are obtained in lessening the intercanthal distance and relieving the epicanthus. He attacks the accompanying ptosis with a levator-shortening through a skin approach, even in the face of little or no levator function. More and more surgeons are of the opinion that a levator-shortening can do no harm and is worth a trial before one of the substitute sources for lid motion is utilized. Hughes creates a lid fold at the time of this phase. This goes a long way in giving these persons a more normal appearance. He brings out that the punctum is often laterally placed, and, if this be so, he creates a new punctum by exteriorizing the lower canaliculus on the inside of the medial canthus and excising the terminal portion of it.

Spaeth[2] discusses the historic aspect of blepharophimosis and reviews various procedures which have been used for its correction. He does not offer a new technique but reviews one which he presented in 1934,[3] which gives the best results in his hands. This is a double Z-plasty, with the arms of the Z in a somewhat different direction from those in the frequently used Blair operation. For epicanthus inversus, which is often a part of the condition, he proposes an S-incision along the lower lid fold, which he closes in an L-fashion to relieve the skin tension.

Spaeth also advises levator-shortening for the ptosis if the muscle is not completely inert. He states that fibrosis of the levator tendon is usually found and that it is seldom

Received for publication, Aug. 31, 1956.

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possible to remove over 5 mm. of it. If the levator is not functioning and if the superior rectus is, he advises that a superior rectus procedure be done. He feels that the nonabsorbable frontalis suture should be used only in extreme cases.

Johnson[4] does a lateral canthoplasty, usually of the von Ammon type, to lengthen the palpebral fissure. He shortens the medial canthal ligament by a tucking procedure, using 00000 braided stainless steel for the suture. He combines this with a Blair operation for the epicanthus.

I have followed most of the techniques advised by these writers and feel that there has been at least some improvement over previous results. In addition, I have tried attaching a buried linen suture to each of the medial canthi and tying them together over the bridge of the nose to shorten the intercanthal distance. Time will tell if the early result will be maintained. I do not feel that the suture will interfere with nasal development significantly.

Ptosis

The work of Berke and others during the previous years has been exhaustive and has resulted in something of a slowdown on ptosis articles during the past year. There have been a few, though, that are contributory to our handling of the problem. Noteworthy is the paper by Schimek.[5] He describes a new operation for ptosis for use when the levator is nonfunctioning or poorly functioning. This procedure utilizes both the levator itself and the frontalis, one enhancing the effect of the other. Here the levator is isolated in the usual fashion. Instead of excision of a section of the levator and its tendon, the terminal portion is divided into two slips. These are passed through two incisions in the superior part of the tarsus from the posterior to the anterior surface. They are then carried through tunnels anterior to the orbital septum and deep to the orbicularis muscle to be attached to the frontalis above the brow. Hence the levator is resected for what spontaneous lid motion can be obtained through its action. Also the frontalis is used for forced elevation. I have used the operation on three occasions. I obtained results better than I had (though poorer than the patients had) anticipated.

Borges[6] presents a technique for raising the lid by means of stainless steel or tantalum sutures fixed to the superior orbital margin through holes drilled in the bony orbit. I will grant that this will elevate the eyelid, but it seems to me to be a rather rigid attachment. I can see no advantage to this over an attachment to the mobile frontalis in the same area.

Two papers (Hendrix[7] and Strampelli[8]) advocate the use of strips of orbicularis muscle as a lid-elevating attachment. Hendrix[7] dissects a 3 mm. strip of orbicularis from the level of the supraorbital rim, carries it down through a tunnel beneath the skin, through a slit in the superior margin of the tarsus, and back up to the level of origin. He reports better results in teenagers and adults than in children. He does not give the indications for this operation, but they must be limited. Strampelli[8] also uses the orbicularis but directs an inferior strip upward around a previously outlined button of skin at the midpoint of the brow. He reports excellent results in 12 patients.

Mikaelian[9] stresses the use of "palpebro-orbital" sutures, which he says can be relied upon if the conjunctival sutures tear out. I had not been aware of this problem.

Sayoc[10] stresses the importance of the formation of a lid fold in any ptosis operation—a factor which is often overlooked. The technique has been previously reported in several journals. He makes a skin incision 6 to 8 mm. above and parallel to the lid margin and excises a narrow strip of underlying orbicularis. After the ptosis procedure he sutures the lower skin flap to the anterior surface of the tarsus with three to five buried sutures. He then closes the skin with interrupted nonabsorbable surgical (silk) sutures.

Along the same line, but not dealing with ptosis, is an article by Millard,[11] who de-

scribes a procedure developed in Korea to change the lid appearance from Oriental to Occidental. He creates a lid fold and obliterates the epicanthal fold with a Z-plasty. He states that the epicanthus in Orientals is not a web of skin but a fold of excess skin. I have many Oriental friends and patients, none of whom has expressed a desire to have Occidental eyelids. I have been told that in the Orient such a desire does exist in many Orientals, and for their benefit this article is of value.

Entropion and Ectropion

There have been a few articles on the subjects of entropion and ectropion during the past year. Wies [12] has reported a simple technique for the correction of spastic entropion. This technique has appeared in other journals prior to this reference. He makes a through-and-through incision the length of the lower eyelid 4 mm. below its border. Three double-armed sutures are placed through the tarsoconjunctival edge of the lower flap and brought out through the skin edge of the bridge. The skin is closed with a few additional sutures. He reports a few overcorrections. McFarlane [13] reported a review of 60 cases treated by the Wheeler, Ziegler, and Wies procedures. He found 56% of the Wheeler and 47% of the Ziegler operations satisfactory, while 78% of the Wies operations gave good results. He says that there are fewer recurrences with the Wies operation. This operation may present a simple solution to a difficult problem. A statistical comparison with the Butler [14] and Fox [15] operations, which have recently become popular, would aid in our evaluation of these techniques.

A most comprehensive review of the surgery of trachomatous deformity of the eyelids comprises the entire second number of the 1956 *International Review of Trachoma*. It is presented by Besnainou,[16] of Tunis. It cannot be summarized in a review of this nature. He describes in detail the various surgical techniques which are used in this regard. He uses the Cuénof-Nataf method for the upper lid in all of his cases now. This consists of an incision 1 mm. deep along the intermarginal line and another through the skin 2 or 3 mm. above the free border. A wedge-shaped strip of tarsus is removed through the second incision. Three sutures are passed into the marginal incision and out through the upper wound. They include a small bite of the tarso-orbital fascia above the convex border of the tarsus before emerging through the upper skin edge. It would be well for any surgeon who treats these lids to read this review. It is in French, but there are English summaries of all important phases.

Three other papers concern the surgical correction of cicatricial entropion and trichiasis. Button and Kader [17] presented a new type of suture in an operation similar to the Hotz-Anagonstakis technique. Diab and Matta [18] describe an operation for the same disease, in which a buccal mucous membrane graft is fitted accurately into an incision through the deformed tarsus parallel to the lid border. The graft is teased into position and left without sutures. They report that in 244 patients less than 1% of the grafts failed to take. Glikson [19] advises tarsectomy of the Kuhnt type, for trachomatous trichiasis, which he modifies slightly. He states that he has done several thousand of these operations, always with excellent results.

Spadafora [20] offers a simplified method of applying a split-thickness skin graft for severe cicatricial ectropion. He relieves the contraction with the usual skin incision and the excision of subcutaneous scar. Rather than do a tarsorrhaphy, he holds the deformed lid in place with a traction suture taped to the cheek in the case of an upper lid. A split-thickness graft is then applied and held in place with a petrolatum gauze splint. No sutures are used. A pressure dressing is applied. He reports good results in five cases. I would fear contraction of the graft in the absence of a tarsorrhaphy.

Vannas [21] also reports on methods of applying split skin and mucous membrane to the lids and conjunctiva. He modifies the Keller and Esser inlay types of grafts. He

places the grafts around x-ray film or thin acrylic stents. The final trimming and careful approximation of the edges is done about 10 days after the placing of the grafts.

The taking of split-thickness grafts from the retroauricular area is facilitated by the use of a small dermatome which uses safety razor blades. This is reported in a paper by Bonola.[22] This instrument, of Argentine manufacture, will take grafts accurately from 0.3 to 0.6 mm. in thickness. In children Bonola advocates 0.3 or 0.4 mm. grafts. In adults he uses 0.5 to 0.6 mm. grafts, the latter being about three-quarter thickness. He states that full-thickness grafts, of 0.8 to 1.0 mm., are too thick for eyelid repair. Many of us who have used full-thickness retroauricular skin with excellent results would disagree, but we would welcome an instrument which would help us to take grafts without the nuisance of having to trim off the subcutaneous tissue.

The above-mentioned three articles from the foreign literature indicate that split-thickness grafts are still being extensively used in these areas. It is my impression that the majority of surgeons would prefer to use full-thickness skin wherever possible in repairing cicatricial ectropion. Adequate donor skin is usually available from the lids of the same or opposite eye. If not, the retroauricular skin forms an excellent source. Supraclavicular skin can be used, but I would consider it in the same light that Bonola considers retroauricular skin, i. e., too thick in its full-thickness form for good eyelid repair. However, infrequently now but very frequently during times of combat, we do see cases of extensive burns where all available good full-thickness donor skin has been damaged. Here the split-thickness grafts are necessary and give fairly good results.

Tumors

Less material than usual on the treatment of eyelid tumors has appeared during the past year. This is a common problem and still one in which there is much disagreement as to the best treatment. An excellent article by Reeh and Hyman [23] has appeared, and I recommend that anyone who attempts the treatment of eyelid malignancies read it in its entirety. Most of us realize that both properly executed surgery and properly given x-ray treatments are equally good in curing basal-cell malignancies of the eyelids. We too often are carried away in our enthusiasm for our own field. This holds true for the radiologists as well as the surgeons. In this article, written by an ophthalmic surgeon and a radiologist, equal emphasis is placed on the value of surgery and x-ray therapy. These authors say that the selection of the method which will completely destroy the tumor with the least amount of functional impairment and with the best cosmetic effect is the goal. They state that inadequate surgery followed by inadequate x-ray therapy is not the answer to tumor treatment problems. They emphasize the importance of biopsy before any treatment is attempted. This would seem to be obvious, but it is neglected unbelievably often. They mention the use of frozen sections but state that they have not found it too helpful. I have been attempting to perfect the use of frozen sections with the edges for section selected and removed by the ophthalmic surgeon. I feel that it can be developed to a point where it can be utilized in obtaining complete removal of tumors with the best possible cosmetic and functional repair.

Reeh and Hyman stress the importance of fractionation and protraction in roentgen therapy and show cases in which excellent results have been obtained. They emphasize the desirability of close cooperation between the ophthalmologist and the roentgenologist in the management of these cases. They advocate a combined x-ray and surgical technique in certain cases of advanced malignancy, by means of which exenteration has in some instances been avoided. Here thorough radiation is given to destroy the malignancy. This is done with the knowledge that severe scarring will result. Following the x-ray treatment by several months, surgical repair of the deformity is carried out. This seems to be an excellent

approach and one which will allow a patient to retain a useful globe, which in some instances treated by other methods would have to be sacrificed.

Renfer [24] feels that x-ray therapy is the best treatment for tumors of the skin of the medial canthus. He stresses the importance of conserving the function of the lacrimal duct. In this regard I have found it useful to keep a length of polyethylene tubing in the inferior canaliculus during x-ray therapy and until the reaction from it has subsided.

Uptake studies of radioactive phosphorus (P^{32}) in intraocular tumors are being investigated, and valuable information is being obtained. In a study of 262 cases of ocular pathology, Terner, Leopold, and Eisenberg [25] included 29 adnexal lesions. Of these 29 cases, there was 1 false negative test in a basal-cell epithelioma of the eyelid. The study of adnexal lesions has investigative value, but, as the authors state, the test "offers the surgeon an advantage otherwise obtainable only by biopsy. In lid lesions the test does not offer as great an advantage."

Smith and Brockman [26] reported on 82 cases of epithelial tumors of the eyelids. They found about the usual distribution, some 58% involving the lower lid, 22% involving the upper lid, and 12% and 8% involving the inner and outer canthi, respectively. They dislike the diagnosis of basosquamous-cell carcinoma, feeling that a true mixed type is exceedingly rare. They feel that almost all cases with this diagnosis are either basal-cell or squamous-cell with some secondary hyperplasia of the other element. They also do not feel that the term "adenoid cystic" hair follicle type of epithelioma represents a true histologic entity.

Whorton and Paterson [27] reported an unusual case of carcinoma of Moll's gland of the upper eyelid which extended intraepithelially to the surface skin of the lid margin. It was microscopically identical with Paget's disease of the breast. It recurred after repeated surgical removals and eventually necessitated exenteration of the orbit.

Primary tumors of the Meibomian gland are rare, and the literature on them is limited. Straatsma [28] discusses them thoroughly. He divides them into benign (hyperplasia, adenoma and hamartoma—a tumor composed of cords and masses of epithelial cells surrounded by a distinctive stroma) and malignant (carcinoma). He reviews 16 cases of the latter. The condition should be considered in any lesion involving the lid margin or producing a mass in the tarsus. The average age in Straatsma's series was 57, with a range of from 20 to 84 years. The tumors were slightly commoner in the upper eyelid. The treatment advised is surgical excision and plastic repair. Regional nodes should be excised, if involved, and x-ray should be given to the area.

Christensen and Fitzpatrick [29] reported a case of keratocanthoma, or molluscum sebaceum, of the eyelid which appears histologically similar to squamous-cell carcinoma. The lesion grows rapidly for six or eight weeks and then regresses. This is similar to the report of Ruedemann and Hoak,[30] who state that molluscum sebaceum cannot be distinguished histologically from squamous-cell carcinoma. They feel that the best treatment for both is probably wide excision.

Inflammatory Diseases

There were several articles on inflammatory lesions during the past year but few on any one phase of these diseases. Wong, Fasanella, Haley, Marshall, and Krehl [31] reported a controlled statistical study on the use of selenium in the treatment of marginal blepharitis in 59 patients. The results were equivocal. Two patients developed a keratitis with conjunctivitis and swollen erythematous eyelids, which cleared with cessation of the drug. They concluded that as good response to treatment was obtained with ammoniated mercury as with selenium. Thygeson and Vaughan,[32] on the other hand, felt that selenium sulfide was the most effective agent in the treatment of seborrheic blepharitis, particularly when the same agent

was used on the scalp. They stress the importance of the presence of Pityrosporum ovale in lid margin scrapings—if not as a causative agent, at least as a diagnostic index and a gauge as to the effectiveness of therapy.

Holmberg [33] reported on pilocarpine sensitivity of the eyelids. He states that skin tests can be negative on the arm and positive on the eyelid, indicating a local sensitivity. He states that conjunctival sensitivities to pilocarpine are more frequent than lid reactions and that both are very rare, considering the number of patients who are using pilocarpine daily.

Bobb [34] described an unusual case of elephantiasis nostras, a solid edema of the eyelids caused by bacterial infection with damage to the venous and lymph drainage channels. A chronic inflammatory fibrosis and hyperplasia of the dermal and hypodermal tissue results. The edema is not the pitting type He treated his case by surgical removal of the skin and subcutaneous tissue. He warns of the danger of an ectropion from excision of too much tissue.

Gaynon [35] reported an interesting case of 4 mm. of unilateral lid retraction which could be attributed only to a chronic meibomitis. He felt that the retraction was due to spasm of Mueller's muscle and the levator caused by the Meibomian inflammation. The retraction regressed under treatment with lid expression, heat, Staphylococcus toxoid, and antiseptics.

Noma of the eyelids is a severe type of moist gangrene seen in malnourished infants. It ordinarily terminates fatally. Pereira and Conti [36] reported such a case, which was unsuccessfully treated with penicillin. Frezotti [37] reported a case of palpebral leishmaniasis which was treated successfully with systemic antimony and without local treatment. Palic-Szántó [38] reported an eyelid lesion which biopsy proved to be lupus erythematosus. The patient was seen four years later, at which time the lesion was still confined to the eyelid.

Maumenee [39] described 13 eyes in eight patients in which a keratitis resulted from keratinization of the tarsal conjunctiva. The keratinization resulted from such conditions as Stevens-Johnson's disease, reactions to medication, x-ray, and eczema of the lids. The keratitis was relieved by surgical removal of the offending epithelium. In some cases a mucous membrane graft from the mouth had to be placed at the lid border to protect the cornea.

Lacrimal Apparatus

Tumors

Tumors of the lacrimal gland have been a poorly understood group of neoplasms. In recent years several papers have been published which help to make some order out of this chaos. Two of these are within the period of this review. Reese,[40] in the seventh Arthur J. Bedell lecture on the treatment of expanding lesions of the orbit, stressed those lesions arising in the lacrimal gland. In an analysis of 112 tumors of the lacrimal gland fossa he found 31% to be granulomatous, mostly nonspecific. He found 24% carcinomatous, 22% mixed tumors, 21% lymphosarcoma, and 2% adenomas. Therefore, about one-third of the lesions were not neoplastic. Of the two-thirds that were neoplastic, 30% were lymphosarcoma and hence nonsurgical. This leaves about 50% of the total of lacrimal fossa lesions which are epithelial tumors and must be treated surgically. Of these, about half are malignant and have an exceedingly bad prognosis. Reese finds the following incidence in the classification that he uses: benign mixed 43%, adenoid cystic (cylindroma) 38%, carcinoma (indeterminate) 11%, malignant mixed 4%, and mucoepidermoid 4%.

Since it is impossible to determine clinically with which type one is dealing, Reese stresses the importance of biopsy. If a pathologic diagnosis of malignant mixed tumor or carcinoma is received, he advises exenteration of the orbit, with removal of bone with which the tumor is in contact.

He proposes an approach which is a combination of the Benedict brow approach and the Kroenlein operation for tumors which can be removed without exenteration.

Milam and Heath [41] present a report on 29 cases of epithelial tumors of the lacrimal gland in order to correlate the histopathology and emphasize the poor prognosis. Their classification varies somewhat from that of Reese. They feel that benign adenomas are exceedingly rare and that most of these lesions are malignant. They say that the tendency to report from histologic evidence that a lesion is benign is dangerous unless it is unquestionably an inflammation or a simple adenoma. Of their 29 malignant cases, followed for varying periods of from 1 month to 28 years, 15 were classified as fibromyxoepitheliomas, and, of these, 4 were lost to follow up, 3 were living without recurrence, 2 were living with recurrence, 2 had died of their tumor, and 4 had died of unknown cause. Eight were classified as basiloma, which is histologically similar to basal-cell carcinoma. Of these eight cases, seven died of tumor and one of unrelated cause. Six were classified as "other carcinoma," i. e., adenocarcinoma, squamous-cell carcinoma, and undifferentiated, or anaplastic, carcinoma. Of these six, three were dead of tumor, two were living with inoperable metastases, and one was living without recurrence. Milam and Heath [41] draw about the same conclusion as Reese [40] does. They state that poor results may be due to undue delay, incomplete biopsy, and inadequate surgery. They make a plea for early and deep biopsy and, if an epithelial tumor is found, exenteration of the orbit with removal of bone in contact with the tumor. Both Reese and Milam and Heath stress the inadequate protection and sense of security that an apparent capsule gives.

Pineiro y Carrion [42] reports a case of lacrimal gland tumor in a 26-year-old man characterized by slight exophthalmos, papillitis, and retinal folds. It was found to be an encapsulated mixed tumor and was removed locally. He advocates that before radical surgery is carried out an anterior approach to the tumor should be done, as this may be all that is necessary. After reading the previous article, I should be hesitant to follow his advice.

Davis [43] reported a case of epidermoid carcinoma of the lacrimal sac in a 39-year-old man with a tender swelling, which could not be expressed, over the tear sac area. The tear channel could be irrigated, but there was epiphora. The lesion was excised and found to be a well-differentiated epidermoid carcinoma. Three weeks later the ethmoids were exenterated. He has been followed for one year without evidence of recurrence.

Inflammatory Diseases

Gruber,[44] in an article reporting a case of sarcoidosis associated with Sjögren's syndrome, brings out the possibility of a common etiological factor of a chronic infective nature in these conditions and Mikulicz's syndrome. In this case he used prednisone, which gave relief of both conditions. Ainslie and James [45] suggest the Kweim test as a specific test for sarcoidosis if lesions for biopsy are not available. The test consists of the intradermal injection of an emulsion of sarcoid tissue in a saline solution. A positive test is a red nodule at the site of the injection appearing in three or four weeks.

Mietke [46] reported a case of cytomegaly of the lacrimal gland. This is a disease of virus etiology which is characterized by large unilocular cells in the salivary glands and parenchymatous organs. These cells contain inclusion bodies. This case was of a 59-year-old woman with recurrent orbital swellings. Typical cells were found in the cirrhotic lacrimal gland.

Infectious mononucleosis is a disease with numerous bizarre complications. One does not often think of dacryoadenitis as one of them. Jones [47] states that painful inflammatory swelling of the lacrimal glands is not a rare complication and emphasizes that the ocular symptoms may overshadow the systemic manifestations to the extent that the diagnosis may be missed.

Inflammatory reactions in the drainage part of the lacrimal system are of course frequent. The treatment of their results makes up the majority of the lacrimal system literature and will be discussed presently. There were a few articles on the etiology of some of these diseases, and three of them are included in this section. Wolter, Stratford, and Harrell [48] made a histologic study on a cast recovered from the lacrimal system of a 23-year-old woman who had suffered from epiphora until its removal and recovery from the nose. It revealed an organism identified as Candida albicans. In a discussion of concretions of the lacrimal passages, Appelmans and Zwijsen [49] doubt the existence of Streptothrix foersteri as a specific variety of fungus. They feel that Aspergillus niger and Actinomyces are the principal offenders. Mamelok and Laval [50] report a case of Stevens-Johnson's disease with a resultant obliteration of the puncta and canaliculi. A 10-year-old boy had been treated with cortisone, among other things, during the acute phase. There were adhesions of the upper and lower lids at the puncta in both eyes one year later. An attempt to reestablish tear drainage with polyethylene tubes was unsuccessful.

Lacrimal Intubation and Dacryocystorhinostomy

The rather voluminous literature which continues from year to year on the treatment of epiphora, with the reporting of both success and failure by one method or another is good indication that our methods are far from perfect. The recent vogue of polyethylene intubation, with the initial enthusiasm and ensuing apathy, is another indication of this dilemma. Improvements in technique and more careful selection of cases may result in better and longer-lasting results.

Valentin-Gamazo [51] reported 15 cases of intubation of the nasolacrimal duct, with but 1 failure. He makes a tear sac incision and places the tube directly into the nasolacrimal duct. He resutures the medial canthal ligament in such a way as to make some pressure over the sac and prevent postoperative ectasia. He states that this procedure is better than dacryocystorhinostomy. Those of us who have not had the best results from introducing tubes through the canaliculi might do well to try this method before giving up this type of intubation.

Dejean [52] states that he now gets almost uniformly good results in intubation by using a tube 2.5 mm. in diameter and 15 mm. in length. The lower end is slightly cone-shaped to facilitate introduction. He enlarges the nasolacrimal canal before introducing the tube, by curetting the mucosal lining.

LeGrand [53] reported 16 patients, with 5 poor results, in his series of lacrimal intubations. This is somewhat better than the results of Vicencio,[54] who reported 16 cases of nasolacrimal duct stenosis with chronic dacryocystitis, with no successes. He used a nylon thread in 10 and polyethylene tube in 6 of his patients. He left these in place for from six days to five months. His criterion for success was not whether lavage were possible but whether epiphora and infection were relieved. Since the patients were not free of symptoms, he reported 100% failure and concludes that dacryocystorhinostomy is still the answer to treatment of stricture of the nasolacrimal duct.

For those who wish for some reason to retain a small polyethylene tube in position for any length of time, the technique of Reese [55] will be of value. He mentions the difficulties in maintaining the tube in position and reports a method of shaping the tube over a stainless steel wire bent to fit the lacrimal system. The tube, bent around this wire, is dipped in recently boiled water to fix the angulation. The wire is then removed and the tube reinserted. The tube bends down from the punctum into the inferior fornix, where it rests without irritating the cornea.

I have used a fair number of feet of polyethylene tubing over the past few years and have come to appreciate its usefulness

in certain instances. I have not become convinced by experience or reading that it is an answer to chronic dacryocystitis due to nasolacrimal blockage. I have found it to be useful in reestablishing stenosed canaliculi in about half of the cases attempted. In this instance, anchoring has been no problem, as a straight piece of tubing will remain in the canaliculus indefinitely, held by the nasal wall of the sac at one end and the bend in the canaliculus near the punctum at the other end.

I have the greatest respect for the operation of dacryocystorhinostomy and am amazed at the high percentage of these that remain patent and give the patients complete relief of symptoms. New techniques are frequently being devised which in their authors' hands give improved results. Juge[56] feels that failures are often due to poor apposition of the nasal mucosa to the sac mucosa and often to the canaliculus being too near to the upper edge of the bony opening. He proposes an operation using the entire sac sutured to a 3 or 4 mm. circular orifice in the nasal mucosa. Cavalheiro-Willmersdorf[57] recommends a technique in which the rubber tip of a dropper bottle is inserted into the bony opening, the mucous membrane flaps being sutured over it. This conformer is left in place for 10 days. These techniques are variations of older methods and are perhaps improvements on them. Duverger and Marsat[58] advise a motor-driven dental burr in making the trephine opening into the nasal cavity. Goodyear[59] decries the complicated operations being used for dacryocystorhinostomy. He reports a modified Toti-Mosher operation in which the nasal wall of the sac is preserved and laid in two flaps into a large bony opening into the nose. No sutures are used except for the skin. Sakic[60] modified the Axenfeld tear sac speculum to include a protecting plate which guards against wounding of the mucosa of the sac during dacryocystorhinostomy.

I have felt that the dacryocystorhinostomy which will most consistently give the best results is one which removes almost all of the infected and dilated sac, has a large enough opening in the bony wall, and has a positive sutured connection between the nasal mucosa and the lacrimal mucosa. There are several operations which fulfill these requirements.

Ashley[61] outlines a method of reconstruction of the lacrimal drainage system which he has used in badly traumatized cases. His longest follow-up is one year, but he reports satisfactory results in six cases. He inserts a length of polyethylene tube across the lid slit and through both canaliculi. The two ends are carried together across a bony opening into the nose. A split-thickness skin graft is wrapped, with raw surface out, around the tubes. I recently had occasion to try Ashley's operation. It was technically easy. When I had finished I wondered why I had not used buccal mucosa instead of skin. Ophthalmologists have for the most part given up the use of skin in replacing mucous membrane. The anticipated results in these badly traumatized cases are not good, and Ashley's contribution seems to be a good one.

Gáll and Brooser[62] state that trachoma often causes stenosis of the lacrimal passages. They state that the points of attack are usually the physiologic narrow places. They believe that x-rays, after the injection of a radiopaque medium, are the only means of accurate diagnosis.

Demorest and Milder,[63] in their second article on dacryocystography, describe some aspects of the pathologic lacrimal apparatus. They state that in a normal sac the radiopaque dye usually disappears within 30 minutes. There are cases of epiphora in which the tear ducts are easily washed and in which the dye is still retained on the 30-minute x-ray. They feel that in these cases the epiphora can be relieved by dacryocystorhinostomy. They state that about three-fourths of the blockages of the lacrimal passages are at the junction of the tear sac and the nasolacrimal duct. They state that when dacryocystography shows a large sac the response to dacryocystorhinos-

tomy is better than when it shows a shrunken sac. They feel that dacryocystography is also useful in demonstrating diverticulae and fistulae of the sac. They recommend the routine use of it in all cases of epiphora. Most of us would hesitate to order radiologic studies on all of our patients with tearing, but if it were feasible and possible to do so our percentage of good results would probably be much higher.

Burch-Barraquer [64] describes a condition which may account for some troublesome epiphora and for the failure of some properly performed operations to give properly functioning results. In some cases, when one irrigates through the lower canaliculus, fluid returns through the upper punctum and some of it passes into the nose. A probe introduced into the canaliculus fails to enter the sac but meets a resistance at the level of the common canaliculus. When the probe is moved in various directions it may find its way into the sac. Burch-Barraquer relieves the obstruction as follows: When the sac is open a probe is passed to the obstruction and with fine scissors a portion of the outer wall of the sac, including any obstructing fold, is removed. The canaliculus opening is enlarged and threaded with a silk suture which is left in place for 15 days. This procedure can be combined with a dacryocystorhinostomy. Starkiewicz [65] has an operation wherein he mobilizes the upper canaliculus and transplants the distal end into the nasal cavity. Thus the tears travel through the lower canaliculus as far as the blocked common canaliculus, then through the transplanted upper canaliculus to the nose.

Congenital Anomalies

Three unusual congenital anomalies are reported. Flom and Levitt [65] report a case of two fully formed lacrimal puncta opening into a normal canaliculus. In the same eye there was a cyst of the lacrimal gland. De Conciliis [67] reports a duplication of both the lower punctum and canaliculus and an absence of the upper punctum and canaliculus. Hughes and Ballen [68] report an unusual case of two finger-like projections onto the cornea, originating in the subconjunctival tissue. The corneal tumors were removed and were found to be well-developed lacrimal gland tissue.

Miscellaneous

Eadie and Thompson [69] treated 12 patients with Sjögren's syndrome with cortisone and corticotropin (ACTH). In the cortisone-treated patients they obtained controls by treating only one eye and comparing the two. They found hydrocortisone locally to have no advantage over cortisone, corticotropin systemically to be no better than local cortisone, and ointment to be no better than drops. They stated that the symptoms were ameliorated but that there was no improvement in the Shirmer test.

Lao [70] reported on a patient with xerophthalmia due to trachoma in which there were no tears. He transplanted the parotid duct into the conjunctival sac, with adequate moistening and some improvement in vision. He gives a detailed description of the operation. There may be some excessive tearing—especially during eating. While a parotid duct transplantation was described by Filatov in 1950, a description of the surgical technique is now available in English.

Solé [71] wrote on the stagoscopy of tears. Stagoscopy is the observation of drops of any fluid. A drop is put on a slide and allowed to dry. The pattern of the dried fluid gives some information as to the chemical constitutents of this fluid. The colloids remain in the periphery, while the salts concentrate in the center. Tears treated in this fashion dry with a small marginal zone consisting of protein while the central area consists of crystals. The author states that the stagogram of human tears is very characteristic.

Erickson, Feeney, and McEwen [72] studied the tear fluid of 20 different animals electrophoretically. They found a great variation in the protein component from animal to animal. Primates showed a "slow moving lysozyme," but other animals showed

none. They state that plasma proteins do not contribute significantly to the protein constituents of normal animal tears.

Conjunctiva

Adenovirus Group, Including Epidemic Keratoconjunctivitis

By far the most significant conjunctival literature during the past year is that concerning the so-called APC, or adenoidal-pharyngeal-conjunctival, group of viruses (now termed adenoviruses). This group was described by Rowe and co-workers [73] in 1953. It is a large group, which is subdivided into serologic types by specific neutralization tests. According to Jawetz, Hanna, Kimura, and Thygeson [74,75] Types 3 and 4 APC virus cause the various symptoms of epidemic pharyngoconjunctival fever; Types 3, 4, and 7 can cause respiratory disease of varying type and severity; Types 1, 2, 3, and 5 cause pharyngitis; Type 6 may cause a follicular conjunctivitis, and Type 8 is probably the causative agent in epidemic keratoconjunctivitis.

Ryan, O'Rourke, and Iser [76] reviewed the characteristics of the pharyngeal conjunctival disease caused by Types 3 and perhaps 4 APC virus. In recent years this disease has been recognized as a distinct entity and is now termed pharyngoconjunctival fever. It may occur in sporadic or epidemic form. It is frequently associated with swimming pool exposure. According to Ryan, O'Rourke, and Iser it may be carried by ophthalmic instruments. They state that fever is present in 90% of the cases, conjunctivitis in 66%, pharyngitis in 70%, headache in 68%, and lassitude or malaise in 72%. The characteristics which they mention include the following:

The incubation period is 5 to 10 days—frequently after swimming pool exposure, which may be in well-chlorinated pools.

The disease is commonest in children but may affect adults.

The disease is self-limited, lasting one to two weeks.

The symptoms may be mild to relatively severe.

One or both eyes may be involved.

The conjunctivitis is acute and catarrhal, or nonpurulent.

The lower palpebral conjunctiva is the most severely involved, but the bulbar conjunctival and upper fornix also are inflamed.

There is hyperplasia of the lymph follicles.

There is no significant corneal involvement, and no membrane or pseudomembrane forms.

No inclusion bodies are found in epithelial scrapings.

Antibiotics and sulfonamides are of no therapeutic value.

Steroids used locally lead to lessening of the symptoms and do not cause danger of exacerbation.

Fowle, Cockeram, and Ormsby [77] isolated a virus from the secretion of the eyes of three persons with keratoconjunctivitis. This virus was found immunologically to fit into Type 3 APC virus. All three of these patients had corneal staining with underlying opacities, which developed at the height of the conjunctival reaction, and preauricular nodes. Two of them developed pseudomembranes. Tissue culture fluid from the fourth passage in monkey kidney epithelium was inoculated into the fornix of a human volunteer. He developed the same disease five and one-half days later, with resultant corneal opacities which slowly regressed.

Sage and Suie [78] reported on five patients with a follicular conjunctivitis during the course of which subepithelial opacities developed and later regressed. In one of these they isolated a virus which was found to belong to Type 3 APC group.

Ormsby [79] reported in the *Canadian Journal of Public Health* on the ocular diseases due to APC viruses in Ontario. Here he states that sera from four patients with epidemic keratoconjunctivitis had neutralizing antibodies to Type 8 APC virus. However, in the most recent epidemic, of 20 patients with viral conjunctivitis, half developed minor corneal opacities. In three

of these a virus was isolated which was found to belong to Type 3 APC virus.

Jawetz, Hanna, Kimura, and Thygeson [74] were the first to relate Type 6 APC virus to a human disease. They isolated this virus from two patients with follicular conjunctivitis and mild respiratory infection.

Jawetz, Kimura, Hanna, Coleman, Thygeson, and Nicholas [80,81] restudied the problem of epidemic keratoconjunctivitis. They state that the most constant clinical features appear to be the following: After an incubation period of 7 to 10 days there develops an intense follicular conjunctivitis with marked conjunctival injection. Often a thin pseudomembrane is formed. The conjunctival involvement, occasionally unilateral, is accompanied by enlarged and tender preauricular lymph nodes. There is a scanty, nonpurulent exudate, with abundant lacrimation. Five to ten days after the onset of conjunctivitis, corneal lesions develop. These are characteristically small round subepithelial corneal opacities, generally without significant superficial ulceration, and without impairment of corneal sensitivity. The number and size of these corneal opacities vary, as does their interference with visual acuity. The opacities disappear slowly in from a few weeks to two years.

This description is somewhat similar to the clinical picture described by Fowle, Cockeram, and Ormsby.[77] However, Jawetz and co-workers [80,81] isolated a virus, from the eyes of a merchant seaman with typical epidemic keratoconjunctivitis and from the eyes of a nurse who became infected while attending him, which serologically belonged to Type 8 APC virus. They obtained blood from 25 patients from four different North American areas who had suffered from epidemic keratoconjunctivitis between 1951 and 1955 and found neuralizing antibodies to the Type 8 APC virus in all of the 25 specimens. It is of particular interest that the sera of the three original patients and the human volunteer reported by Fowle, Cockeram, and Ormsby [77] were tested and did not contain antibodies to this Type 8 APC virus.

Thus it appears that both Types 3 and 8 APC virus cause a form of epidemic keratoconjunctivitis. The diseases are serologically different, though certainly clinically very similar. Further investigation may prove which has been the recurrent offender in the various outbreaks in different areas of the world.

Arakawa, Ohashi, and Seki [82] carried out an experimental study on epidemic keratoconjunctivitis. They claim that they can isolate the virus from both the conjunctival scrapings and blood of patients suffering from the disease.

In the field of therapeutics, Ohashi [83] treated six patients with early epidemic keratoconjunctivitis with hyperimmune rabbit serum and felt that it shortened the course of the disease and prevented or minimized corneal opacities.

Hofman [84] stated that 99% of 200 patients with epidemic keratoconjunctivitis in Austria developed corneal lesions on the fourth or fifth day of the disease. He believes that the local application of convalescent serum, potassium permanganate, and the use of nonspecific fever therapy are the most useful treatment methods.

The large amount of investigative work that has established the existence of the adeno (APC) group of viruses, the isolation of the various types, and the establishment of their etiologic relationships to the known diseases has done and is doing much to increase our knowledge not only of that group but of the general field of virology. This field is becoming more and more important in disease. Therapeutic success is the ultimate goal.

Trachoma

Most of us who practice in this country see only an occasional case of trachoma and tend to minimize its importance. However, it continues to be the major eye disease of the world in spite of the advances in treatment during the past 20 years. The World Health Organization [85] considers it one of their major problems. The trachoma index in some areas of the world approaches

100%. Since such conditions exist and since world travel is becoming so simple and so popular, we can expect to see more than an occasional case and should be well versed in the methods of diagnosis and treatment. Only in this way can we prevent visual loss and spread of the infection.

From the Russian literature comes a report of the cultivation of the trachoma virus. Kogan-Abezgus [86] claims that it is possible to cultivate trachoma virus on chick embryo from active proved cases in from 6 to 16 passages. He reports positive results in the complement-fixation reaction with blood from patients with advanced and complicated trachoma. The blood serum from normals and from patients with early trachoma usually gave negative results. This is an interesting report but should be confirmed by other investigators before it can be accepted. The virus should produce typical trachoma in a human volunteer before its identity can be definitely established.

Hidehisa [87] made photographs with the electron microscope of a conjunctival tissue suspension from a trachomatous patient. Virus-like particles 60 to 200 mμ in size were found. In addition, there were many clusters of these of 400 to 700 mμ in size, which would be visible to the light microscope. He feels that these may be what are recognized as elementary bodies.

The presence of inclusion bodies in trachoma scrapings is said to be less frequent now than in the past. Dark [88] states that inclusion bodies are easier to demonstrate in thin smears of conjunctival epithelium than in scrapings. He says Giemsa is the best stain. Dark was able to demonstrate nucleic acids and carbohydrates in the inclusion bodies by histochemical methods. Thygeson [89] states that the cytologic findings in conjunctival scrapings in order of importance in trachoma are (1) inclusion bodies, (2) Leber cells, (3) germinal center follicle cells with degenerative changes, (4) plasma cells, and (5) multinucleated epithelial cells. In follicle expressions the findings of importance are (1) Leber cells in numbers, (2) degenerated germinal cells, (3) cytoplasmic debris, and (4) greater numbers of lymphoblasts than other monocular cells. He says that the finding of inclusion bodies limits the diagnosis to trachoma and inclusion conjunctivitis.

Litricin and Pavlovitch [90] made a study of the area of the inferior orifice of the nasolacrimal duct in trachomatous patients and found pathologic changes which they felt were due to descending infection. No inclusion bodies were found. Postic [91] attempted to inoculate the mucous membrane of the mouth with trachomatous material but was unable to create a definite reaction except for a few follicles. He feels that follicle formation is not a specific symptom of trachoma but that the necrosis and scarring which occurs in the conjunctiva is.

The incidence of trachoma in Japan is clearly shown by a careful study by Matunga, Asakage, and Kunitomo.[92] In a town of 26,000 with a known trachoma index of 12% they examined and followed the eyes of 102 newborn infants for a period of 18 months. During this period 96 were found to have a conjunctivitis of some kind. An acute onset was noted in 17 of these cases, and 2 of these 17 were found to have trachoma. The onset was subacute in 76 instances, and of this number 62 developed follicles and 44 of these developed symptoms characteristic of trachoma. In 24 of these, inclusion bodies were demonstrated. In the remaining cases the onset was insidious and no cases of trachoma developed. Hence, in this study 24% of the infants developed proved trachoma and another 20% developed what appeared to be trachoma during the first 18 months of life. It is of interest that the Expert Committee on Trachoma of the World Health Organization [85] considers that most cases of trachoma are of insidious onset.

Sztrilich [93] found a correlation between the incidence of trachoma and helminth infection. He stated that both trachoma and helminthiasis bear a close relation to general hygiene and that it is in this regard that they are related to each other. He feels

that trachoma responds better to treatment if the helminthiasis is also treated. Sédan [94] noted improvement without treatment in a group of trachomatous African children during a sojourn in Normandy. He felt that the geographic change was less important than was the change of hygienic conditions.

An interesting epidemic of trachoma of some 15 years ago in Breslau was reported by Rumbaur.[95] An ophthalmologist had an undiagnosed case of trachoma in his own eyes, which went unrecognized for several months. More than 300 patients were known to be infected from this source. The first symptoms noted by the patients were smarting and photophobia. The first sign was often a slight but definite ptosis. Within a few days injection appeared in the upper fornix, and soon typical follicles developed. Epidemics of eye infections emanating from ophthalmologists' offices are probably more frequent than are reported.

There has not been much new in the treatment of trachoma during the past year. Agarwal, Saxena, and Gupta [96] reported further on the use of antibiotics and the sulfa drugs. They say that erythromycin is the best of the antibiotics but that any of the other antibiotics tested (oxytetracycline [Terramycin], chloramphenicol, and chlortetracycline [Aureomycin]) will rapidly clear the secondary infection. They tested two sulfa drugs, sulfacetamide and N-(3,4-dimethylbenzoyl)-sulfanilamide (Irgafen), and feel that they are about equally effective. They state that the antibiotics work rapidly but that the sulfonamides, though slower, are more effective. In another paper Agarwal with Malik [97] reported on tetracycline used orally and locally in the treatment of trachoma. Forty per cent of the cases showed disappearance of inclusion bodies from the smears in about three weeks. They reiterate the superior effectiveness of the sulfonamides but feel that tetracycline is useful in combination with them. The same conclusion was reached by Pavkovic-Burgarski and Cvetojevic [98] in regard to chlortetracycline. They found it most effective when given combined with oral sulfonamides.

Mezquita, Rabadan, Amerigo, and Osorio [99] used oxytetracycline and chlortetracycline locally in the treatment of 174 cases of trachoma. They were able to cure only 46.8% with oxytetracycline and 38.3% with chlortetracycline.

Bietti and Pannarle [100] reported on the use of a slowly absorbing penicillin preparation which requires an injection only once in two or three weeks. They recommend its use in some cases where frequent observation and supervision is impossible.

These reports from various areas of the world are in agreement that the antibiotics cannot replace the sulfonamides in the treatment of trachoma and that we cannot rely on local treatment with any drug. If trachoma is to be cured we must use oral sulfonamides and we can supplement their action with local antibiotics.

Bacterial Conjunctivitis

The changing picture in the sensitivity of organisms to the various antibiotics and sulfonamides continues. New agents are constantly being tried when the older ones fail to produce results. Suie, Havener, and Sroufe [101] carried out in vitro experiments on staphylococci recovered from 115 cases of conjunctivitis and found the following susceptibilities in the higher concentrations: nitrofurazone (Furacin) 100%, bacitracin 86.8%, tetracycline 78.2%, chlortetraycline 76.4%, chloramphenicol 72.6%, oxytetracycline 67.9%, neomycin 64.8%, dihydrostreptomycin 63.4%, penicillin 62.6%, erythromycin 56.3%, and polymyxin B 7.5%. The high degree of sensitivity to nitrofurazone and the low degree of sensitivity to erythromycin are impressive. An unusual strain of Staphylococcus was isolated from the lower cul-de-sac of a 9-day-old infant with an acute blepharoconjunctivitis by Suie.[102] This strain was completely insensitive to any of the antibiotics, 10 of which were tested. A nitrofurazone disc produced a 24 mm. zone of

inhibition. Except for the rather high percentage of sensitivity reactions to nitrofurazone (up to 4%) which we see, it would appear to outclass the antibiotics by a wide-margin in the treatment of staphylococcic infections. The strains resistant to erythromycin seem to be increasing rapidly.

Hallett, Wolkowics, and Leopold [103] reported on the use of Neosporin in various external eye infections. In its ointment form it is bacitracin, neomycin, and polymyxin B, while in its drop form it is gramicidin, neomycin, and polymyxin B. They report that both preparations were successful in most cases of Gram-positive infections and in all cases of Gram-negative infections. Most viral diseases improved slowly during the course of treatment. They report a local reaction rate of only 0.5%.

Ainslie [104] reported in the *British Journal of Ophthalmology* on the use of Polyfax, which is an ointment containing bacitracin and polymyxin B. He states that there is no antagonistic reaction between the two and that both Gram-positive and Gram-negative organisms are highly susceptible to the combination. Resistance to polymyxin by sensitive organisms rarely develops, and resistance to bacitracin can be developed only with difficulty. Ainslie advises its use proplylactically following injuries. He noted no allergic reactions.

Quiroz, Boyes, and Sacks-Wilner [105] reported on the use of a new preparation termed N.F. 12, which, in addition to neomycin and gramicidin, contains thimerosal, an antihistiminic (thonzylamine hydrochloride), methylparaben and propylparaben, an emulsifier (Pluronic F-68), a vasoconstrictor (phenylephrine hydrochloride), and propylene glycol. It is buffered to pH 7.4 and thickened with methylcellulose (Methocel). It was used successfully in 35 of 37 cases of conjunctivitis, in 6 cases of keratoconjunctivitis, and in 2 cases of conjunctival allergy. The authors felt that it was safe and effective for use in most external ocular infections, allergies, and postoperative reactions.

Theodore [106] used sulfadicramide (N^1-dimethylacroylsulfanilamide) (Sulfirgamide) in 200 patients with conjunctivitis and other external infections. He reported both 7.5% aqueous solution and 15% ointment to be effective. He reported good results in inclusion-body conjunctivitis but not in other viral diseases. He felt it to be a good preparation for bacterial conjunctivitis. He suggests that it be tried as an antitrachoma agent. There appears to be little tendency to allergy with sulfadicramide.

Huntsman [107] has shown that gonorrheal conjunctivitis has not ceased to exist in this country. He reported 45 cases of ophthalmia neonotorum at the Los Angeles County Hospital since 1944. He recommends that both eyes be treated from the first. The eyes should be kept clean with saline, and a penicillin solution containing epinephrine should be instilled every five minutes. Systemic medication is reported to be unnecessary.

Walch [108] recommended that silver nitrate continue to be used prophylactically in the newborn rather than penicillin. He feels that penicillin should be reserved for infections and that its general use as a prophylactic agent would increase the number of resistant strains of organisms. Schultze and Hartmann [109] state that in the venereal clinic at Bremerhaven 21% of the gonococcal strains were resistant to penicillin. They agree that penicillin should not be used in this regard. Zimmer and Kremser [110] reported on 665 newborns in whom all ocular prophylaxis was abandoned. In 45% of the cases a nonspecific suppurative conjunctivitis developed. They feel that silver nitrate should continue to be used, as under this treatment only about 20% showed any irritation and it was usually mild.

Wachter and Pennoyer,[111] on the other hand, feel that erythromycin is superior to silver nitrate in prophylaxis in the eyes of newborn infants. Erythromycin ointment was used in 7110 instances, with fewer conjunctival reactions and with less severe reactions than silver nitrate. They felt that it is equally as effective or more effective

than silver nitrate in protecting against gonococcal infection.

Havener [112] is of the opinion that bacterial conjunctivitis will respond to most of the antibiotic drops available when they are instilled at one- or two-hour intervals. He feels that cortisone is useful in allergic conjunctivitis but contraindicated in viral disease.

Horwich and Fedukowicz [113] reported on variations in the morphology of the Morax-Axenfeld Diplobacillus. They state that this Gram-negative organism is unstable and can be made to assume a variety of forms according to its environment. It may resemble the Diplobacillus of Petit, the Micrococcus of Mitsui, and numerous other organisms.

Suite [114] studied the organisms causing bacterial conjunctivitis in central Ohio. He found Staphyloccus albus and aureus in the majority of cases, with a rather high percentage (16.6%) of Gram-negative organisms.

It would appear that before treating conjunctivitis it is well to know what the causative agent is—at least to the separation of viral, bacterial, and allergic. This can usually be done without elaborate, expensive, and time-consuming procedures. The symptomatology and clinical appearance and the examination of a smear stained with Giemsa stain should be sufficient in most cases to suggest the proper course to follow. It is the exceptional case which should require cultures and sensitivity tests. However, one should not hesitate to use these when indicated. The recent appearance of novobiocin (Cathomycin), an antibiotic appearing highly effective against the prevalent strains of Staphylococcus, is welcome. We await its availability in ophthalmic preparations.

Allergy

A rather comprehensive symposium on ocular allergy was presented at the 59th annual session of the American Academy of Ophthalmology and Otolaryngology, in New York, in September, 1954. This does not lend itself well to review. It consists of three papers, one by an allergist,[115] one on laboratory studies,[116] and one on the clinical aspects in the differential diagnosis of external allergic diseases.[117] Waldbott [115] considers the commoner external allergic conditions from the standpoint of the allergist, with special reference to therapeutics. He states that blepharitis is not infrequently due to food sensitivity. He feels that some cases of hordeolum and chalazion are allergic in origin. Some cases of obstruction of the tear duct may be caused by allergic edema of the conjunctiva. Vernal catarrh is an allergic condition which Waldbott says is due to a combination of sensitivities to fungi and tree pollen. It frequently precedes the onset of hay fever. He speaks of elimination diets, desensitization, counteracting of focal infections, and symptomatic treatment with cortisone, corticotropin, and antihistaminic drugs.

Hanser [116] explains the laboratory techniques and their interpretation. He uses the Hansel stain for eosinophils. He emphasizes the value of a complete history and skin and conjunctival tests for possible allergens.

Theodore [117] feels that allergic blepharitis does not appear to be an entity. He classifies conjunctival allergies into (1) acute allergic conjunctivitis; (2) allergic dermatoconjunctivitis; (3) chronic allergic conjunctivitis, in which he includes the atopic and the bacterial type, and (4) vernal conjunctivitis.

Theodore feels that vernal catarrh has too many of the characteristics of allergy to consider it otherwise—yet no material allergen has ever been shown to cause the disease. He assumes that it is a form of physical allergy to the warm season, occurring in an especially predisposed atopic person.

A comprehensive review of the histories of 1050 patients with vernal conjunctivitis was given by Alimuddin.[118] He found positive allergic histories of the ear, nose, and throat; skin, or gastrointestinal systems in about 14%. Thirty-five per cent had intes-

tinal infestations with roundworms or hookwarms or amebae, and he felt that treatment of this resulted in some improvement in the vernal conjunctivitis. He emphasized that a change to a cooler climate is the best treatment. If this cannot be done, the local use of epinephrine, antihistamines, or the steroids is indicated. Of these, the conjunctiva has the least chance of becoming insensitive to the steroids, and he feels that these are the best drugs to use. He warns against the use of radiation.

Merté [119] treated six children with vernal catarrh with a polyvalent mixture of antigens of staphylococci, streptococci, and tubercle bacilli. Desensitization was followed by a period of three years without recurrence in four of these children.

Vernal catarrh continues to be a perplexing problem. Certainly we are keeping our patients better controlled with the steroids and antihistamines than we were previously able to do. What the long-term results will be remains to be seen.

Allergy to medications instilled in the eyes is common to all of us. Fedukowicz, Wise, and Zaret [120] reviewed the clinical picture of this condition. They state that smears will reveal Corynebacterium xerose (Bacillus xerosis) and toxic basophilic granules in the monocytes present. They feel that these cases are becoming commoner with the use of antibiotics and suggest that their routine use be discontinued in favor of sulfa drugs. As mentioned previously, under Bacterial Conjunctivitis, some of the more effective antibiotic combinations rather recently available have an extremely low allergy index—perhaps lower than have the commonly used sulfa drugs.

Allergic local reaction attributed to the systemic use of hydralazine (Apresoline) in the treatment of hypertension was reported by Thomas, Algan, and Guidat [121] in two cases. Follicular conjunctivitis appeared soon after the drug was used and regressed when it was discontinued.

Symblepharon

An amazing operation for total symblepharon in the presence of an existing eye was presented by Pagani.[122] After re-creating the fornices by dissection, he replaced the conjunctival sac with the entire conjunctival socket of a cadaver, including the superficial layers of tarsus and cornea. The donor material can be aseptically removed and kept in a moist chamber at 2 C for up to 10 days. He maintains the corneal element in place with four human hair sutures. He places traction sutures in the fornices to prevent shrinkage and also utilizes a conformer. He states that in about four days the conjunctiva begins to take on a "living" appearance. The operation is not offered for visual function, but the author suggests the possibility of a perforating or lamellar keratoplasty as a second procedure. Several years ago Dr. Michael Hogan and I removed the entire conjunctiva of a patient with cancerous melanosis and replaced it with a vaginal mucous membrane graft. We were successful in avoiding exenteration, in maintaining all fornices, and in providing a not too good or too bad substitute for conjunctiva but not in retaining vision, as the cornea became opaque and vascularized. This patient has shown no sign of recurrence in six years. Perhaps cadaver conjunctiva would have been a better graft than genital mucosa. Since corneal grafts take so well, it is not unreasonable to expect a relatively avascular tissue such as conjunctiva from autopsy sources to take well. This might prevent the use of some of the red buccal mucosa which we frequently see transplanted to replace bulbar conjunctiva.

Semeraro [123] describes a technique of suturing a piece of rubber between the raw surfaces after lysis of a symblepharon. He removes the rubber after 14 days.

Miscellaneous Conjunctival Diseases

The treatment of burns of the cornea and conjunctiva has been reviewed by Pillat.[124] He recommends that emergency treatment by irrigation with 500 cc. of warm saline solution be carried out. After cleansing, a 10% solution of 1-(*p*-hydroxyphenyl) -2-methylaminoethanol tartrate (Sympa-

tol) is instilled every 15 minutes for 4 to 6 hours, then every hour for 48 hours, every 2 hours for 48 hours more, and then 4 times daily for 2 days. He states that Sympatol is a vasoconstrictor. He feels that it increases the permeability of the vessel walls to blood plasma and red blood cells and hence supplies protein to the damaged tissues. He states that by this treatment scarring, symblepharon, and pseudopterygium are far less than with any other treatment that he has tried. Apparently phenylephrine (Neo-Synephrine), tetrahydrozoline (Tyzine),[125] or other vasoconstrictors would work on the same principle.

Xerophthalmia in its advanced stages is rare here but is probably not too difficult to diagnose clinically. Agarwal and Malhoutra[126] have made a cytologic study of conjunctival smears in early to late cases of xerosis. They state that the normal conjunctival smear shows 10% goblet cells and 45% each of cylindrical and polyhedral cells. In early xerosis the percentage of goblet cells diminishes, and this is a much more reliable sign than is the presence of keratinization. Complete absence of goblet cells is a late feature. They state that epithelial xerosis is a vitamin A deficiency but that if a person with trachoma has a vitamin A deficiency he develops a parenchymatous xerosis.

A membranous conjunctivitis and a superficial keratitis occurring in a child with recurrent aphthous stomatitis was reported by Appelmans and Michiels.[127] Chlortetracycline did not result in any improvement. Iodine cautery gave better results, and aluminum sulfate drops seemed to promote healing of the conjunctivitis.

A case of essential shrinkage of the conjunctiva in epidermolysis bullosa hereditaria was reported by Shah and Shah.[128] There were subepithelial slits in the conjunctiva observed by slit lamp, as opposed to the intraepithelial slits which are seen in pemphigus.

Oppel[129] described a massive thickening of the conjunctiva in an 8-year-old boy who had had a chronic conjunctivitis for six years. Biopsy showed a hyaline and amyloid degeneration of the conjunctiva.

Bowen's disease, or intraepithelial epithelioma of the cornea and conjunctiva, is reviewed by Locke.[130] He reviews 18 cases and states that in 6 of these the disease had its origin at the site of a previous corneal lesion such as a scar or ulcer. Four of the patients had cancerous growths elsewhere in the body, denoting a tendency to malignant tumor formation. Locke states that local excision with about 1 mm. of free border is all that is necessary in most cases. If they recur, the second excision is no more difficult than was the first. Lugossy[131] advises excision of epithelial plaques because of their tendency to carcinomatous degeneration.

Schardt[132] presents a case of lymphosarcoma of the conjunctiva and states that the prognosis is not necessarily bad if the eye is the primary site of the disease and the lesion is thoroughly treated. He sites McGavic's series of 20 cases, in which 5 were alive 16 years after the primary treatment and 5 had died an average of 15 years later of other causes. The other 10 had died of lymphosarcoma. A rapidly growing conjunctival tumor in a 71-year-old man was found to be a lymphosarcoma on biopsy by Friedman, Borrelli, and Geleris.[133] There were no other evidences of the disease. It regressed rapidly after 6600 β r given by the strontium applicator. These cases emphasize the importance of biopsy prior to treatment of any suspicious tumor about the eye.

Heydenreich[134] reports that after repeated subconjunctival hemorrhages the lymph vessels of the conjunctiva may remain blood-filled for a long time. The segmented ampulliform pattern of the blood is characteristic, as is the location in a deeper conjunctival stratum than is occupied by the conjunctival blood vessels.

An interesting case of conjunctival myiasis was reported by Simison.[135] He removed several larvae of the sheep nasal botfly from the conjunctival sac of a young

adult. This is interesting in that it occurred not in the tropics, where it might be common, but in Pocatello, Idaho.

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Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

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Harold W. Brown, M.D., Secretary

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

Bernard Kronenberg, M.D., President
Leon H. Ehrlich, M.D., Secretary

Combined Meeting, Jan. 16, 1956

RECENT ADVANCES IN OCULAR SURGERY

DR. MAYNARD C. WHEELER: The panel of experts is Dr. Milton L. Berliner, whom you all know; Dr. John Gipner, head of the eye department of the University of Rochester; Dr. R. Townley Paton, whom you all know, and Dr. Harold G. Scheie, professor of ophthalmology at the Univesity of Pennsylvania. You all have copies of the questions that we intend to ask these experts. The plan is to direct a question to one member of the panel, but we hope the others will add any comments they wish to or will take exception to the opinion of the first speaker. We hope that we shall have a few arguments.

Dr. Berliner, will you begin by discussing recent advances in scleral shortening for detached retina?

DR. MILTON L. BERLINER: When we look over the statistics of the classic diathermy operation, we find high variations in the percentage of cures. In some cases and in some places men have reported as high as 90% cures (favorable cases) and in others as low as 50% (all types). Perhaps if we take all the cases together (so-called good and bad), the proportion of cures with the classic diathermy operation would be about 65%. Linder, Weve, Kronfeld, and many others realized this many years ago; so it appeared that from 30% to 35% of cases treated by the classic procedure of retinal separation were doomed to failure. These questions arise: What are these bad cases? How do they become so? How are we going to handle them? I think these bad cases can be divided into two main groups as far as their pathogenesis is concerned: One relates to the age duration of the detachment; the second, to our method of treatment. I feel that the age, or duration, of detachment has not always received the importance that it should have; the reason for this is that we do not always get a satisfactory history about the duration of detachment. I have had many cases in which the first symptom was seeing flashes, with vitreous opacities. We think first of detachment of the posterior surface of the vitreous. It is true that spontaneous detachment of the vitreous is only rarely followed by detachment of the retina, but in cases of detachment of the retina one almost always finds detachment of the posterior face of the vitreous. I am thinking of a patient of my own, a man who came in with these symptoms, in whom I found a vitreous detachment. He came back and still had some of the symptoms. It was only after he came back the fourth time two months later, that I was able to find a tear in the retina, the retina itself being only very slightly elevated. When a patient says, "I lost my vision Friday or Saturday," it does not signify that he just developed the detachment on that day. The condition may have been there for two or three months, and it does not take very long before the changes in the separated retina and vitreous develop which turn these cases into so-called bad cases.

Another factor in the production of the so-called bad case, those which we make bad, is overtreating with diathermy, either surface or penetrating. In addition to the danger of creating new breaks, such treatment may pro-

duce retinal and vitreous alterations in which, with release of the subretinal fluid, the retina no longer can get back to the choroid. Because of this, it was soon realized that the only hope in treatment of these cases was in shortening the sclera. As you know, this originally was done by desection of the sclera through its entire thickness; I am not going to go into the complications of total scleral resection; it is a difficult operation (especially as a secondary procedure), with great danger of rupture of the choroid and loss of vitreous. So it came about, although Lindner did mention briefly that he had tried inversion of thinned sclera and had abandoned it, that it was not until 1949 that Shapland, of London, described lamellar scleral resection, or the buckling operation. He was the first who did the operation in the manner in which we now understand it. He applied caustic to the layer of sclera remaining behind. Then Paufique modified the operation by applying the diathermy to the resected area. In 1952 I wrote a paper introducing lamellar scleral resection to this country. This operation has been modified by Schepens, who suggested the use of a polyethylene tube as an aid to buckling. I have employed the tube on occasion, but I am not sure how much it adds to the efficiency of the operation.

The action of the lamellar scleral resection is twofold: First, it permits (nearly) direct treatment to the choroid and, second, it causes an infolding of the choroid, so as to allow closer contact of the treated choroid with the retina. I think it is much better to treat the choroid as directly as possible than to do it by treating the surface of the sclera. Application of diathermy to the total scleral thickness results in large areas of destruction, not only in the sclera and choroid but also in the retina; very frequently, as you know, we may close the original hole and the patient comes back in a few weeks with a new break in a distant area, owing to traction. Schepens brought out the danger of creating new tears with perforating diathermy. I still feel that lamellar scleral resection is the best procedure because here is an operation in which, first, one can treat an extensive area without creating excessive damage, and, second, because it is possible to obtain a good inverted choroidal roll.

Lately we have seen an additional change in technique, a sort of outward pleating of the sclera, in an attempt to shorten the sclera. I have had no experience with it; therefore I allow myself the luxury of a theoretical criticism with this particular operation. The questions I would like to ask are these: First, with the outward buckle, do we get as good a choroidal roll, and, second, by this method are we able to treat the choroid directly? I think that is going to be the ideal way in which we shall have to treat these bad cases. This procedure, by the way, sprang up in the minds of three men apparently almost simultaneously—Gayles, of Marseilles, who reported the operation at the meeting of the French Ophthalmological Society last spring; Everett, and Castroviejo. With this method we still have to use either surface treatment or perforating treatment. My feeling is that lamellar scleral resection, which gives a closer approach to the mentioned ideal, is at the moment the best operation for bad cases of detachment of the retina.

DR. MAYNARD C. WHEELER: Do the other members of the panel wish to add anything?

DR. HAROLD G. SCHEIE, Philadelphia: I am not as enthusiastic about scleral resection as many persons here tonight. I should like to ask Dr. Berliner how much his over-all results have improved since he has been doing scleral resection.

DR. MILTON L. BERLINER: I would say they have improved about 15%. In the last four years I have been doing lamellar scleral resection as a primary operation except in the cases in which I felt I could not get to the disc side of the tear or hole. In these cases I had to resort to the classic diathermy procedure. I base my opinion on the fact that the chance of turning a good case into a bad one is less when I use this procedure than when I use ordinary diathermy.

DR. JOHN GIPNER, Rochester, N. Y.: I think that in cases of long-standing detachment my results have improved with lamellar scleral resection. In recent detachments I do the orthodox diathermy retinopexy.

DR. R. TOWNLEY PATON: I think one of the things that has come out of this method is that we can get patients out of bed much sooner. I had a case recently in which I let a patient go home three days after the operation, with good results; with the other method, I do not think this could have occurred. I believe the buckling operation is here to stay.

DR. MAYNARD E. WHEELER: *Dr. Gipner, what do you consider to be the most important recent advances in cataract surgery?*

DR. JOHN GIPNER, Rochester, N. Y.: The most important recent advances cataract surgery are these:

1. The cosmetic and functional improvement resulting from round-pupil intracapsular extractions.

2. Procedures which have increased the safety of the operation, such as (*a*) adequate sedation preliminary to surgery, (*b*) extraocular muscle immobilization and lid akinesia, (*c*) production of a soft eye by retrobulbar muscle cone injection, and (*d*) use of corneoscleral sutures, which permit monocular dressing and early mobilization of the patient.

I think all these procedures which I have listed as advances in cataract surgery are generally used, and I shall see what happens.

DR. MAYNARD C. WHEELER: There is no argument; you have mentioned the things we all seem to agree upon.

DR. JOHN GIPNER, Rochester, N. Y.: Someone at the dinner tonight mentioned the use of Thorazine as a preoperative drug to quiet the patient; I have not used it, and I should like to hear from someone who has.

DR. HAROLD G. SCHIEF, Philadelphia: I consider the introduction of Thorazine to constitute one of the most important recent advances in anesthesia for ocular surgery. I believe it is of great value in all types of intraocular surgery. We have been using it for some months, giving 25 mg. on the day before surgery and 25 mg. three times during the day of operation. This potentiates the action of barbiturates and permits reduction of their dose, usually by one-half. On this regimen an irrational or excitable patient is rarely encountered, and I believe it ensures a smoother postoperative course.

DR. MAYNARD C. WHEELER: *Dr. Patton, will you discuss recently developed measures for the improvement in results in keratoplasty?*

DR. R. TOWNLEY PATON: I think one of the important things that has occurred in this country is the education of the public. The surgeon has a much easier time in dealing with his patients because they do not expect miracle operations in people who are totally blind. Second in importance, I think, is the improvement in technique and in instruments and their application. Another great advance—we always have to refer back to Dr. Castroviejo—is early operation. Success has increased as we operate earlier in all these cases, and that includes the therapeutic graft, either penetrating or lamellar. Much improvement has been made in the selection of cases suitable for operation.

One thing which has not been adequately reported is the use of the emergency transplant in accident cases, or in chemical burns. This opens a whole new field of investigation, and it means that donor material must be available at once in order to operate on the patient. I anticipate many eyes being saved in the future from emergency corneal transplants.

Another recent development is the use of annular or ring-segment grafts in the treatment of marginal corneal dystrophies, Mooren's ulcers, and so forth. I think that in the future we shall have sufficient accumulated knowledge to enable us to operate on these cases, so that if we have a Mooren's ulcer in one eye, and we see it beginning in the other, we shall not hesitate to do a partial annular graft, either penetrating or lamellar, to prevent the ulcer from spreading.

I think the use of cortisone has been of tremendous help. There is some disagreement as to how soon after operation the cortisone should be started.

It is felt by some that the healing process is delayed, but certainly many cases have been saved in which the graft has begun to be cloudy in the second or third week after operation and cortisone therapy has brought back the transparency.

The use of Diamox (acetazoleamide) is of tremendous value in patients having corneal transplants, in reducing the edema, and in one instance that we know of, in which we did a total transplantation and we had a slight incarceration of the iris on the 10th day, the use of Diamox even brought about a retraction of the iris and final closure of the wound.

One other thing which I think brought about our improvement in keratoplasty is our knowledge of donor material. I am sure that in the future possibly the greatest advance, aside from improvement in technique, will be the increased knowledge of donor material. It is now reported that with the newer methods of freezing donor material may be kept several weeks.

With the step graft and the mushroom graft I have not had much experience. In 1911 Carrell and Abling, working on cat eyes, on the preservation of tissue, used the step-graft method to hold the tissue in place, and I believe the step graft will have a great advantage in some cases. It is not a difficult technique; I have practiced it myself on eyes in the Eye Bank, and it may open up new fields of investigation.

DR. MAYNARD WHEELER: Is the lamellar graft of any use in recurrent pterygium?

DR. R. TOWNLEY PATON: It all depends on the case. I think in some cases the double-bladed-knife technique is superior to the use of two trephines. It all depends on the extent of the ptergium. In the treatment of pseudopterygium the use of the annular graft has been very helpful. The technique I have used requires two trephines of different sizes. Suppose this is the surface of the eye; by using a 10 mm. trephine, one can press on one edge so that one does not contuse the whole cornea in making the lamellar incision. We do the same thing with the second trephine, and, with a caliper, we can cut out a lamellar section without endangering the healthy cornea. I think use of the double-bladed knife in some instances can be superior.

DR. MAYNARD WHEELER: *Dr. Scheie, have there been any recent advances in the surgery of chronic simple glaucoma? What is your preference?*

DR. HAROLD G. SCHEIE, Philadelphia: I am delighted that this question was asked, because of its importance and a ready answer. To my mind, the greatest single advance in the surgery of chronic simple glaucoma is the trend toward conservatism. Most ophthalmic surgeons today agree that the diagnosis of chronic simple glaucoma no longer serves as an indication for operation. The two prime indications should be an ocular tension which is fairly constantly 35 mm. Hg or more, or loss of field, which, we know, is due to the glaucomatous process. My colleagues and I recently have reviewed our glaucoma records and have found several cases of bilateral glaucoma of equal severity in the two eyes in which only one eye had been operated on years previously. The eye which had been operated on was all too often lost, blind, or with poor vision from cataractous changes, while the fellow eye which had been treated medically had suffered no loss of vision. Operative, immediate, and late postoperative complications, and failure to control tension, all present obstacles. I therefore urge deferring surgery as long as possible, obviously, not allowing the eye to go blind through neglect, but operating when true indications exist.

Any other advances in this phase of opthalmology, in my opinion, are somewhat nebulous. Possibly the use of hormonal therapy for eyes which are inflamed during the first two or three days after surgery may have increased our incidence of successful filtering operations. The less postoperative reaction, the higher is the percentage of successful filtration.

My operation of choice probably is iridencleisis, although I do a certain number of trephinations on eyes with wide-open angles; this brings to mind another advance in the surgical management of glaucoma represented by preoperative gonioscopy. Fewer and fewer surgeons are doing corneoscleral trephinations in eyes with narrow angles; instead, they are reserving the procedure for eyes with

wide-open angles. An iridencleisis can be done in eyes of either type. Cyclodiathermy, in our hands, has not provided the answer to chronic simple glaucoma but is of some value as a secondary procedure when other operations have failed, or in cases of advanced glaucoma in which conventional operations are hazardous. Cyclodiathermy is an extremely safe procedure when done 6 mm. or more back of the limbus.

DR. MAYNARD C. WHEELER: *Dr. Berliner, what are the indications for the cyclodiathermy operation in glaucoma?*

DR. MILTON L. BERLINER: I am glad to have this opportunity of following Dr. Scheie because he has taken some of the load in answering this question. Unquestionably, cyclodiathermy will reduce the intraocular pressure. The question is, How long will it last, and exactly when should we use it? This procedure is not new; it was used over 75 years ago in France, where they spoke of cauterization of the ciliary body. There have been 180 papers written on the subject. In the last few years there has been a revival of interest in it, and I became interested in it because I found that a great many men abroad, owing to the complication of intraocular surgery, were trying to find refuge in this simple procedure. When I came back, I found Castroviejo was doing the operation, and, using his technique, I decided to run a series. In going over our cases at the Infirmary, I was unable to draw any conclusions from the materials we had collected there over the years because the operations were done by a great many men, each doing a few cases, and the treatments were done anywhere from 2 to 12 mm. behind the limbus. There was no uniformity in the size of the needle or the curren employed, and the follow-up was not all it should have been; so I could not use that material. I therefore decided to collect a number of cases in my own private practice, which I could keep under close supervision, and I told these people: "This is a procedure I am going to do; it is not exactly an operation; it is a sort of treatment." I feel perfectly justified in saying this because in the 150-odd cases in which I have done the operation I have not had one complication. The patient has the operation; he walks home the same day with his eyes open, or possibly he may be kept overnight and go home the next morning with no dressing. In this series I have selected early (good) cases. We all know that in functionless eyes, if we do enough cyclodiathermies, we can lower the pressure; all that is done to convert a hard eye into a soft (?) one. We hesitate to do surgery nowadays; but I remember when, as soon as the diagnosis of glaucoma was made, no matter what stage the disease was in, we operated. Now most of us try to go as long as we can without surgery. I tell my patients that this procedure may not work, and that they may have to have an intraocular operation later, but I explain why I am doing it. In the series which I reported on at Buffalo at the state meeting last spring, I had 53 eyes, of which 60% were of the open-angle type, and the others were of the narrow (closed)-angle type. In most of these cases we have had gonioscopic examinations; I am not always 100% sure whether I am dealing with a closed angle or not. Sometimes it is difficult to tell, and we have to use the darkroom test or do tonography to help in making the decision. This series of patients has now been carefully observed for three and a half years. In 17 cases I have repeated cyclodiathermy twice, and in 3 of those 17 cases I had to do an iridencleisis. I think I can safely say that in 50% of the cases in which I have carried out the procedure I have been able apparently—and I say "apparently" advisedly, for we know glaucoma is a progressive disease and there are probably varieties of types which we may not be aware of—in 50% of the cases to hold the pressure down for three years. Next year I may have to change my mind. I hope to watch the patients for the next five to seven years and see how they get on, for someone might ask, "How do you know that these cases could not have been kept under control medically without the cyclodiathermy?" I cannot answer that; but in this series, so far, 50% have been controlled, and most of them had their base pressure lowered to less than 23 mm. and have not lost vision or field. Whether the case is a narrow-angle (closed-angle) or an open-angle type, if the tension can be reduced to between 15 and 20 mm. the progress of the condition may be arrested. I can only give you what I know from my own experience, which is not great; but I think the matter will bear watching in the future, and I hope to be able in the

next two to three years to report on what has happened to the cases that are now under control.

DR. R. TOWNLEY PATON: I should like to ask whether you think this procedure is a risky one in the cases with an aphakic eye.

DR. MILTON L. BERLINER: I have had some cases in which the field is within 5 degrees of the fixation point, and I have never yet had an immediate loss of central fixation after cyclodiathermy. I have had cases of secondary glaucoma after cataract extraction in which I have reduced the tension with cyclodiathermy; these cases seem to be arrested; in a few the vision went down to 20/50, possibly due to fibrosis or other changes which occurred, but the pressure is down, and, although there is some loss of vision, the disease seemed to remain stationary.

DR. MAYNARD C. WHEELER: *Dr. Gipner, what is your approach to cataract surgery in the presence of corneal dystrophy?*

DR. JOHN GIPNER, Rochester, N. Y.: In the presence of mild corneal dystrophy, such as early Fuchs' dystrophy, the incision should be made in the sclera behind the limbus in a shelving manner, so that the chamber is opened just behind the root of the iris. This can only be done by a slow scratch dissection, as in doing a cyclodialysis. The bleeding is controlled by epinephrine-soaked cotton sponges and pressure. The incision is kept much shorter than the regular incision. A complete iridectomy and removal of the lens by the Verhoeff or Kirby modification is done. Care is taken to avoid injury to the posterior corneal surface by not introducing instruments into the chamber. The wound is tightly closed with corneoscleral sutures, and the chamber is partially filled with air. Vitreous must be kept away from the cornea, and, should the chamber collapse, prompt air injection into the chamber is necessary.

If the patient has advanced cataract and severe Fuchs' dystrophy, so that keratoplasty must be considered, the transplantation should be done first. If lattice or nodular dystrophy is severe, a lamellar keratoplasty can be done before or after the cataract operation. Corneal opacity and secondary dystrophy resulting from postoperative contact of formed vitreous with the posterior surface of the cornea can be corrected, even if present a year or more, by vitreous drainage and freeing of the adhesion, followed by air injection into the anterior chamber, as recommended by Leahey. The clearing of the cornea following this procedure may be remarkable.

DR. MAYNARD C. WHEELER: *Dr. Paton, what are the indications for keratoplasty in children? What was the age of the youngest patient you operated upon?*

DR. R. TOWNLEY PATON: The reason that more children are not operated on is the great difficulty in postoperative management. In the case of a child of 3 or 4, you practically have to give a general anesthesia in order to get a look at the eye, and there certainly is danger of infection when you do not look at the eye for a week or 10 days, as is often the case; but I believe that in future more children will be operated on. Our youngest patient was a child of 2 years, in whom a lamellar transplantation was employed for a densely scarred cornea. Only a slight improvement resulted. Another child, of 3 years, was given a lamellar transplant, first in one eye, and then in the other, in which there was scarring from nonsyphilitic keratitis. In going over the literature, I have come to feel that more children should be operated on, for the condition is very similar to the type for which we operate in older people, and it stands to reason that complete amblyopia would have been prevented had we operated on many of these children earlier.

Other indications for operating on children are emergency measures, such as might result from severe burns and perforating ulcers.

DR. MAYNARD C. WHEELER: *Dr. Scheie, will you discuss the relative merits of goniopuncture and goniotomy in infantile glaucoma?*

DR. HAROLD G. SCHEIE, Philadelphia: My first presentation on goniopuncture was made in this hall. It, therefore, is only fair that the ghost should return to haunt me at the same place. I have operated on a series of patients, using goniotomy on one eye and goniopuncture on the other, reserving goniopuncture for the worst of the two eyes. The results have indicated that either operation can effectively control the ocular tension in infantile glaucoma in approximately

50% of eyes as a primary procedure. Since the number of patients operated on in this manner of controlled study was small, actual percentages are not too meaningful. The fact that each procedure can be effected immediately raises the question as to the mechanism of action of these operations and revives a very old argument, which dates back to 1893, between di Vincentiis and de Wecker regarding the mode of action of goniotomy. Di Vincentiis believed goniotomy exerted its action by debriding the angle and restoring normal drainage of aqueous through the canal of Schlemm. De Wecker, after a visit to di Vincentiis' clinic, did the procedure and wrote an article, entitled "Internal Sclerectory," in which he stated that the operation was effective through incising the inner layers of the sclera, which permitted the escape of aqueous through intrascleral venous channels, and possibly absorption by episcleral vessels. This argument has never been resolved. The fact that goniopuncture does control tension by producing a fistula and that it is effective as a primary procedure in approximately the same percentage as goniotomy reinforces the opinion of de Wecker but does not prove it. Postoperative gonioscopy on patients who have had goniotomy reveals clefts in the angle wall of a significant number. It is impossible to say whether or not they are fistulae; just as one cannot with finality say that microscopic fistulae might not exist even when not seen by gonioscopy. The final answer awaits future studies. However, since one operation may work by debridement and the other by filtration, I often combine the two procedures into one by doing a goniopuncture upon completing the sweep of the knife for the goniotomy. The results to date seem better from the combined operation than they seem to be from either alone. Whether this is because production of a fistula is more certain or whether it is due to the additive effect of two mechanisms I cannot answer.

DR. MAYNARD C. WHEELER: *Dr. Berliner, what is your experience with keratome vs. knife section in cataract surgery?*

DR. MILTON L. BERLINER: For the first 25 years of my ophthalmological life I used the Graefe knife and never thought I would use anything else, but five or six years ago, when we were hunting for the ideal type of corneoscleral suture, I decided to follow Dr. Kirby in making a fornix based fllap, and also using 000000 absorbable surgical sutures to close the corneoscleral wound; that is when I started to use the keratome section. As a result, I think I have not had, from a practical standpoint, any more flat chambers, propapses of the iris, or epithelial downgrowths than before. I think I have had less since I have been using the keratome. It is very important that one should have very sharp instruments. I use the Grieshaber keratome and Castroviejo's curved scissors in enlarging the wound. Another important point is to make very short snips; I think the chance of getting a smooth circular cut is greater if one takes numerous very fine snips with the scissors. Any trouble one has is probably related to the placement of sutures rather than to the incision.

DR. MAYNARD C. WHEELER: What is the experience of the rest of the panel?

DR. JOHN GIPNER, Rochester, N. Y.: I use the keratome; I used to consider myself a very good Graefe knife man, but I have used the keratome for many years now. I have always thought one good cut with the scissors was better than three or four short ones.

DR. R. TOWNLEY PATON: I use the keratome, and I think it is due to the fact that we all use more preplaced sutures. I use three sutures, and I think we are fortunate here in New York in having good assistants to help keep these sutures out of the operative field.

DR. HAROLD G. SCHEIE, Philadelphia: We use the keratome and scissors and prefer it to the Graefe knife, although I originally learned to do cataract extractions with a Graefe knife. I agree that the most important factor in wound healing is the type of wound closure used, not the type of incision. Good work can be done with either.

DR. MAYNARD C. WHEELER: *Dr. Gipner, will you compare needling versus linear extraction for congenital cataract?*

DR. JOHN GIPNER, Rochester, N. Y.: Modern linear extractions for soft congenital cataracts are replacing the older operations, such as multiple needlings,

the Ziegler through-and-through operation, and the Moncrieff operation. It was commonly thought that a simple needling was much safer than a linear extraction, but this idea is no longer tenable. Simple needling often required a secondary linear extraction if glaucoma developed, and the end-result of multiple needlings was often a late-developing retinal detachment. With the modern technique of limbus-based conjunctival flap, keratome incision, peripheral iridectomy, air injection, and buried corneoscleral sutures, we have the advantage of restoring vision to the infant or child rapidly and safely. The Barkan-Cordes operation can be done if a shelving corneal keratome incision is preferred. The danger of anterior adhesion of the iris to the corneal section, in spite of air injection into the anterior chamber and prolonged atropinization, leads me to favor the first-mentioned technique.

DR. BERNARD KRONENBERG: *What are the indications and results in keratoplasties in the presence of corneal dystrophy, Dr. Paton?*

DR. R. TOWNLEY PATON: Very probably this is the field where we have made our greatest advances in keratoplasty. At the symposium held in Chicago at the meeting of the American Academy of Ophthalmology and Otolaryngology in 1948 there was not a single case of Fuchs' dystrophy in which transplantation was considered a success. There had been two cases reported in which the graft had remained transparent for a few months. We now have on record at our hospital cases of Fuchs' dystrophy which have been carefully followed for as long as two years, and in one case over six years, in which the graft has remained clear and good vision has been maintained. Statistics now show that when cases are operated on early one may expect good results in 30.8% of cases.

The lattice and grumous dystrophy give a very favorable prognosis. Statistics show that 85% do well. The type of corneal dystrophy or bullous keratitis following cataract surgery gives, on the whole, poor results. In general, the best we can hope for is to make the patient more comfortable. Occasionally a lamellar transplantation done in these cases gives some visual improvement.

In regard to doing a cataract extraction in cases of Fuchs' dystrophy, I do not agree with Dr. Gipner. From my experience it makes no difference whether the cataract section is corneal or scleral; the important thing is to extract the cataract with the least amount of damage to the posterior layers, especially to the endothelial layer. The fact that corneal transplants are successful in some advanced cases of Fuchs' dystrophy would lead one to suppose that it is the amount of damage done to the remaining healthy endothelium which is the determining factor.

DR. MILTON L. BERLINER: I would like to add a word to your observation that making a scleral incision does not prevent the progress of corneal dystrophy after cataract. We have made the scleral incision in several cases, going back 2.5 mm., and these cases (endothelial dystrophy) all went on to opaque cornea just the same.

DR. JOHN GIPNER, Rochester, N. Y.: To my mind, I think the important thing is not to traumatize the cornea in the operation, and I think it can be done with the posterior incision, a small incision, or in the regular routine manner, provided one does not pull the cornea back or rub the posterior surface of the cornea. Nobody has had enough cases to prove this point. Dr. Paton can probably prove this better than anybody else; but it seems to me that if one stays away from the cornea, one will be less likely to injure it.

DR. BERNARD KRONENBERG: I would like to hear something about your experience with corneal transplantation in the herpetic type of keratitis.

DR. R. TOWNLEY PATON: This brings up a very interesting and controversial subject. In general, I agree with Dr. Gundersen, of Boston, that topical cortisone is contraindicated either pre- or postoperatively; on the other hand, intravenous corticotropin has helped some of these cases immeasurably. I have Dr. Cole to thank for this advice after seeing a most dramatic cure of one of his patients. Since then I have used the drug in a number of cases in which grafts were done during the active stage of the infection, with most encouraging results.

DR. BERNARD KRONENBERG: *Dr. Scheie, will you discuss the surgical management of juvenile glaucoma?*

DR. HAROLD G. SCHEIE, Philadelphia: Juvenile glaucoma, by arbitrary definition, is primary glaucoma occurring at any age from that of children just beyond the time when buphthalmos occurs, up to 30 years of age. The operation of choice is goniopuncture. It is simple, nonmutilating, and quite safe. It can be repeated one or more times, after which, if the tension is not controlled, the more mutilating, conventional procedures, such as iridencleisis or corneoscleral trephination, can be done. Goniopuncture does not interfere with the effectiveness of these measures, especially when it is done in the lower half of the circumference of the eye, leaving the upper half undisturbed and unscarred for future surgery.

The eye has a normal appearance to ordinary inspection after goniopuncture. However, gonioscopy demonstrates a small opening in the corneoscleral wall at the site of the puncture, and a very filmy, diffuse edema of the overlying conjunctiva is discernible with a slit lamp. I believe it is the safest of all filtering operations. In a small series it has successfully controlled the ocular tension in approximately 60% of eyes with juvenile glaucoma.

DR. BERNARD KRONENBERG: Do you think operation should be done as late as possible in these cases?

DR. HAROLD G. SCHEIE, Philadelphia: I would be more inclined to operate on juvenile glaucoma early. The chance of preserving vision in these young patients throughout life without operation is quite slight.

DR. MILTON L. BERLINER: Have you had any experience with cyclodiathermy in juvenile glaucoma?

DR. HAROLD G. SCHEIE, Philadelphia: I have had none. However, in this country the results from cyclodiathermy in infantile glaucoma have been poor, in the experience of Shaffer, Barkan, Haas, and others.

DR. BERNARD KRONENBERG: *Dr. Berliner, what surgery do you advise for chronic dacryocystitis?*

DR. MILTON L. BERLINER: I think there is no longer any excuse to do a dacryocystectomy, except when one expects to find a tumor of the sac, or possibly in a very old person with a cataract in his eye, when one is in a hurry to remove the cataract or is in fear of residual infection. I think a dacryocystorhinostomy is the most accepted treatment of this condition, especially since two new advances have appeared. One is the use of the Stragker saw, with the guard; despite the fact that it cuts through bone, it will cut through mucous membrane if you push a little bit, but if you use the guard it will be fairly safe. The second advance is the use of the polyethylene tube. I leave it in the nose for three or four weeks after the operation, with a little adhesive on each end to fasten it to the face; the patient is taught how to manipulate it daily. After three or four weeks we withdraw the tube and start irrigation, and we have obtained extremely good results; the ducts have all stayed open with that method. There are other points in doing the operation which do not belong to the question: One should operate low down so as not to get into the sinuses and should make the hole in the bone large enough.

DR. BERNARD KRONENBERG: *Dr. Gipner, what type of corneoscleral sutures do you use in cataract surgery?*

DR. JOHN GIPNER, Rochester, N. Y.: My patients and I have had more comfortable and pleasanter postoperative experience since I began burying the corneoscleral sutures under the conjunctiva. The patients no longer complain of suture-knot irritation unless the ears of the knot are cut too long and an end erodes through the conjunctiva. I am relieved of the necessity of deep-suture removal, which many times became a more dreaded experience than the actual surgery itself. If one resorted to the use of lid akinesia, the procedure became a second operation to the patient.

Our method of suture placement is as follows:

1. Limbus-based flap dissected free of subconjunctival bands down over the limbus.
2. Small keratome section.
3. Enlargement of keratome section with scissors so that the combined section

is about 6 or 7 mm., adequate to work with in placing two sutures at 11 and 1 o'clock, with no danger of the flap sliding laterally.

4. Appositional radial sutures placed while the conjunctival flap is folded back over the cornea. Use of a good forceps is important here.

5. Completion of the section with scissors. A single cut on each side usually suffices.

6. Spreading the loop of sutures to each side in preparation for the peripheral iridotomy.

7. At close of operation sutures are tied and cut short; the conjunctiva is closed with a running 000000 mild chromic suture, the remainder of one of the corneoscleral sutures.

DR. HAROLD G. SCHEIE, Philadelphia: I still use silk; I do not like to work with chromic.

DR. BERNARD KRONENBERG: Why do you prefer silk?

DR. HAROLD G. SCHEIE, Philadelphia: Silk is more flexible; it is finer; it is easier to work with, and it is easier to identify under the operating light. I have used chromic as a supporting or supplementary suture but have been under the impression that it is more irritating than silk.

DR. MILTON L. BERLINER: I do not agree with Dr. Scheie about not using chromic absorbable surgical sutures; I think it is as satisfactory as silk, and I have not used silk for many years. I have had no trouble from the absorbable type, no infection or cyst difficulty, and it is a great relief not to have to remove sutures. We use absorbable surgical sutures with a knot at the end of it. I have always felt that if one puts in a preplaced suture and has to close the eye in a hurry, by the time you make two movements you are too late.

DR. BERNARD KRONENBERG: It is true that there are as many sutures as ophthalmologists.

DR. HAROLD G. SCHEIE, Philadelphia: Closing the wound can be accomplished equally quickly with either nonabsorbable (silk) or absorbable sutures, but the choice depends greatly upon the type of wound closure that is employed.

DR. R. TOWNLEY PATON: One argument against the absorbable surgical suture: We have used it a number of times, sufficient to show me, at least, that this is not the suture to use in transplants. It would seem that it would be the ideal thing, because many of our complications occur at the time of the removal of sutures, no matter how careful we are. We found with absorbable surgical sutures that at the end of 21 or 30 days there are still little bits of the suture material which are irritating, and that if the patient comes from out of town stitch abscesses may develop.

DR. JOHN GIPNER, Rochester, N. Y.: I agree with Dr. Paton, absorbable surgical (gut) sutures should not be used on the surface of the cornea. Silk is best for corneal suturing.

DR. BERNARD KRONENBERG: *Dr. Paton, when should a patient with keratoconus be operated upon?*

DR. R. TOWNLEY PATON: I think nearly all patients with unilateral keratoconus should be operated on. In general, it used to be said that anyone who had vision of 20/200 or less when wearing contact glasses should be operated on. I think we now agree that as soon as the patient is not able to wear contact glasses, regardless of the degree of vision, he should be operated on, and if the condition seems progressing rapidly, so that there is a frequent change in the contact glass, an indication that the condition is not stationary, the sooner one operates the better. One must be sure there is no glaucoma present!

DR. BERNARD KRONENBERG: Dr. Paton, would you like to say a word about the size of the transplant?

DR. R. TOWNLEY PATON: My own feeling, if I were having my eyes operated on, would be to have a small graft done on the first eye, and, if that was successful, when it came to the operation on second eye, to have a larger graft done; this would result in less of a refractive error. All the donor eyes are contaminated; we do not know where the eyes come from; we know they are contaminated, for cultures are made; if an infection sets in and the graft becomes cloudy, it is better if the first penetrating graft is a 6 mm. graft than if it is an 8 or 9 mm.

one. In many severe cases of keratoconus reoperation may have to be done at the end of 10 or 15 years, since the graft tends to thin out in the central area.

DR. BERNARD KRONENBERG: *Dr. Scheie, will you discuss recent advances in anesthesia in ocular surgery?*

DR. HAROLD G. SCHEIE, Philadelphia: The use of Thorazine pre- and postoperatively represents one of the most important advances in anesthesia for ocular surgery. Dr. Atkinson, who is well known for his work in anesthesia, contributed greatly to the avoidance of orbital hemorrhage after retrobulbar injections by devising a blunted needle for this purpose. The trend toward using larger amounts of procaine for facial blocks represents another advance in local anesthesia. Castroviejo, Atkinson, and I, and other surgeons, have followed this trend. I inject 20 cc. of 1% procaine hydrochloride for facial akinesia with the aim of infiltrating a large area. The result is as nearly 100% effective as any technique can be. No ill-effects have been observed over a period of eight years because procaine causes almost no local irritation and the total amount of porcaine employed is well within the limits of safety. An injection of 5 cc. is made by the usual method for the O'Brien block, 5 cc. at a 45-degree angle downward, 5 cc. at a 45-degree upward over the zygomatic arch, and, finally, 5 cc. along an area halfway between the hair line and the orbital rim, as far as the needle will reach. The block is similar to one I have seen Castroviejo use, and which has been suggested by Atkinson, in which a comparable amount of anesthetic solution is injected from anteriorly, the needle being inserted just behind the lateral orbital margin.

Another advance in local anesthesia seems imminent in the form of anesthesia of sufficient long duration to prevent postoperative pain. Most patients have pain of some degree following intraocular surgery. It begins one to two hours after operation, when the anesthetic begins to wear off, and lasts for another 8 to 12 hours, or slightly longer. Pilocarpine instilled after cataract extraction greatly increases the incidence and severity of postoperative pain. During the past two years, we have had made available to us, by Upjohn, a new anesthetic known as U-0045, which is effective for as long as 12 hours. As yet, it is not available commercially, because it is somewhat too irritating to employ in the large amounts necessary in general surgery. Manufacture for its restricted use in retrobulbar anesthesia is prohibitive. It has a different chemical composition from the procaine group of drugs, preventing rapid destruction by the tissues. Because of its duration, it does prevent most postoperative ocular pain. Although it is not yet available, its importance may rest in helping to open avenues for the development of others, possibly chemically related and more practical.

More recently I have been interested in a method of prolonging retrobulbar anesthesia by employing a fine polyethylene tubing, which is retained in the muscle. It has been used safely in over 300 patients. Polyethylene tubing is widely used in nearly all fields of surgery and is known to be nonirritating. The method is effective because pain is relieved almost instantaneously by the injection of anesthetic solution through the tubing. The injection can be repeated when needed. It is also helpful in the management of acute congestive glaucoma when the tubing can be left in place until medical treatment is effective or until operation is done. It is particularly helpful in the management of youngsters with secondary glaucoma when repeated paracenteses are required. The tubing can be left in place for a week or more with no ill-effects. Retrobulbar anesthesia can then be achieved without the necessity of repeatedly inserting a needle, which might be impossible in a youngster, and general anesthesia is avoided. All the patients in whom the method has been used have received antibiotics, but this is our routine practice for 72 hours after intraocular surgery.

DR. BERNARD KRONENBERG: *Dr. Berliner, what are the indications for the use of the erisiphake in cataract surgery?*

DR. MILTON L. BERLINER: I might be facetious and say, "the presence of a cataract"; but, actually, if you look at the lens with the biomicroscope and see a swollen lens, which you can tell by finding opaque material behind the lens capsule, or if you find the specular reflex (chagrin) missing, you may suspect

that you have a taut capsule and you may have trouble grasping it with a forceps; unquestionably, I think it is easier to grasp the anterior capsule with the erisiphake, but even the erisiphake offers no guarantee that you will not rupture the capsule. If we are honest, we shall all have to agree with Holland, in India. He admits to breaking 30% of capsules and to almost 2% loss of vitreous. I think you are justified in using the erisiphake when you have a swollen lens. The difficulty with the small erisiphake is that one does not obtain very strong suction; so it tends to slip off. You can always put it back on again, sometimes two or three times. With the mechanical types of erisiphakes, the pumps, another factor comes into play, for now we are dealing with a machine, and we have to be very careful in dealing with machines. The rubber tubing may not be the right type, or may be worn out and collapse, in which case we are applying no suction to the lens at all. I once had the experience of thinking I had the capsule, and then, when I started to press with the Smith hook, the lens dislocated into the vitreous, and I had to loop it out. Many men are using the erisiphake exclusively today. I feel the capsule forceps still has a place, but I think the intumescent lens is where I would try it as a first indication.

DR. BERNARD KRONENBERG: What is the opinion of the other members of the panel?

DR. JOHN GIPNER, Rochester, N. Y.: I think if you operate on a very soft eye, you will usually use the erisiphake, because it is much easier to apply the erisiphake on a very soft eye. It requires a new technique to use a capsule forceps on a soft eye. In your extraction you exert much more pull; you do not employ much counterpressure, but merely use the hook to keep the cornea up against the lens as it is being extracted, either by sliding or by tumbling.

DR. R. TOWNLEY PATON: An erisiphake should be present on the instrument table at all times, as one never knows in advance when one might have to resort to its use. As a rule, I use the hand erisiphake in all hypermature cataracts. I find the small Bell erisiphake quite adequate and see no reason for using a motor-driven one.

DR. BERNARD KRONENBERG: *Dr. Gipner, what are your indications for round-pupil extractions?*

DR. JOHN GIPNER, Rochester, N. Y.: Practically every extraction is done by the round-pupil method. Formerly I did a complete basal iridectomy in glaucoma and cataract cases, but found that peripheral iridectomy following dialyzing of the iris base was adequate and better, inasmuch as miotics could be used more effectively if needed. In dystrophy cases, where a scleral section is made, iridectomy is performed. If formed vitreous should be lost, the iridectomy is made complete. If the iris should happen to be drawn back under the sclera with the vitreous after extraction of the lens, it is left alone. The iris at 6 o'clock is cut radially to prevent a drawn-up, hammock pupil. In occlusion and seclusion of the pupil from old uveitis, complete iridectomy may be necessary to break the adhesions of the iris to lens capsule with the spatula. Peripheral iridectomy prevents pupil-block glaucoma in round-pupil intracapsular cataract extraction.

DR. BERNARD KRONENBERG: Do you believe the visual results are better in round-pupil extraction than with total iridectomy, or does the round pupil flatter the surgeon's ego?

DR. JOHN GIPNER, Rochester, N. Y.: I think they are definitely better.

DR. HAROLD G. SCHEIE, Philadelphia: I am not convinced.

DR. R. TOWNLEY PATON: I think it depends on the case for operation. I feel that the round-pupil cataract extraction should be considered a standard procedure, but there are many contraindications, especially in those cases in which the pupil is not, or cannot be, well dilated. Great damage may be done in trying to remove the lens in these cases unless an iridectomy is performed.

DR. MILTON L. BERLINER: The only way I have by which to judge this would be cases in which I did an iridectomy on one eye and a round-pupil extraction on the other in the same patient, whether it is psychological or not with the patients, they say, "This round-pupil eye feels and sees better."

DR. BERNARD KRONENBERG: *Dr. Paton, what are the advantages of a lamellar transplant over a keratectomy?*

DR. R. TOWNLEY PATON: Keratectomy is indicated where extensive vascularization is present in densely scarred corneas and as a preliminary measure before attempting lamellar transplantation.

DR. BERNARD KRONENBERG: *Dr. Scheie, how would you manage a patient with cataract and chronic simple glaucoma* (a) *at age of 40 years;* (b) *at age of 60 years?*

DR. HAROLD G. SCHEIE, Philadelphia: I have sufficient difficulty with all cataracts associated with glaucoma that they need not be complicated further by dividing them into age groups. The question is difficult to answer in a generalized way. I would, however, be more inclined to operate on an eye for glaucoma prior to cataract extraction in a patient 40 years of age than I would be in a person of 60. Otherwise their management is identical. You have all had, I am sure, trouble with the older patient who cannot use miotics because of his cataract, but that would be true also of the 40-year-old man, so that I believe discussion from that point of view is unimportant. The 40-year-old patient with longer life expectancy would demand much more careful consideration of the management of his glaucoma than the 60-year-old man. For example, if the tension of a patient of 60 years was maintained at 30 to 35 mm. Hg (Schiøtz) by miotics, he could probably have a cataract extraction done without glaucoma surgery beforehand. If the 40-year-old man were in a similar situation, I would advise glaucoma surgery prior to the extraction. Time does not permit a detailed didscussion of the many other factors which are involved.

NEW YORK ACADEMY OF MEDICINE. SECTION OF OPHTHALMOLOGY

Maynard C. Wheeler, M.D., Chairman
Harold W. Brown, M.D., Secretary
Regular Meeting, Feb. 20, 1956

Scleral Support with Metal Rings in Intraocular Surgery. DR. G. BONACCOLTO.

The most important factor in the prevention of vitreous prolapse in cataract surgery is the avoidance of pressure upon the globe. If this pressure can be prevented, much will have been accomplished toward ensuring a satisfactory lens extraction.

Throughout the years, when the development of the ideal procedure for extraction of the lens was being explored, many methods and instruments were devised, the most important of which were (1) akinesia of the seventh nerve supply to the orbicularis muscle by the block method of O'Brien (*Arch. Ophth.* 1:447, 1929) or the Van Lint technique (*Ann. ocul.* 151:418, 1914); (2) retrobulbar injection of procaine into the extraocular muscle cone; (3) employment of curare to paralyze the orbicularis and extraocular muscles; (4) use of traction sutures to the lids, and (5) application of various blepharostats, none of which is suitable for all types of eyes.

Professor van der Hoeve, of Leyden, originally used four sutures placed in the sclera between the limbus and the insertion of the rectus muscles in order to prevent loss of vitreous (*Klin. Monatsbl. Augenh.* 62:791, 1919). The van der Hoeve sutures, however, could not guard against loss of the shape of the globe, and the procedure was therefore abandoned.

In 1946 Dr. Flieringa, of Rotterdam, introduced an ingenious method of maintaining scleral support by means of metal rings. With this technique the compressing effect on the globe by the extraocular muscles is minimized and actually transformed into useful forces which maintain an ideal scleral rigidity and contour for the satisfactory performance of an intraocular procedure. (*Am. J. Ophth.* 35:1618, 1953).

The device is of the utmost simplicity and consists of a fine, rigid steel ring about 0.5 mm. in thickness. Three sizes are at present being manufactured in the Netherlands (18, 20, and 22 mm., by Avedko Handelmaatschappij c.v. Dordrecht).

Technique

The usual Van Lint lid akinesia is administered, and retrobulbar injection may or may not be given.

A ring of appropriate size is selected and anchored to the sclera at the 10, 2, 4, and 8 o'clock positions by 000000 black silk sutures, using preferably Grieshaber needles.

Then, four bridle sutures with 0000 black silk are passed at the four cardinal points. Each of these sutures is knotted over the ring and anchored with clamps on the face mask so that they remain attached at the corresponding four cardinal positions. This results in an even suspension of the ring, at the same time maintaining the normal scleral contour.

The cataract extraction is performed according to the surgeon's method of choice (Bonaccolto, G.: *Am. J. Ophth.* 28:1335, 1945; in Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, Philadelphia, Lea & Febiger, 1948, p. 753).

The use of the scleral rings in a series of cataract extractions has convinced me of their value in preventing possible vitreous presentation or loss during the operation and in facilitating the corneal section, placement of sutures, delivery of the lens, and the appositional closure of the sclerocorneal and conjunctival wounds.

I am also impressed by the fact that, after the corneal section was made and the keratome withdrawn, the anterior chamber, which usually completely collapses, was still partially formed. This, to my mind, meant that there was no slight increase in the intraocular pressure, which would generally cause complete emptying of the anterior chamber.

Throughout the postoperative course of these cases in which the scleral rings were used, there was perfect closure of the conjunctival and sclerocorneal wounds, ensuring the maintenance of a formed chamber.

The pupil remained round and centrally placed from the first day, and there was absence of striate keratitis.

Summary

A metal ring device is described which maintains effective scleral rigidity and contour of the globe for intraocular procedures.

Satisfactory cataract surgery without vitreous loss was performed in a series of cases with this form of scleral support.

Discussion

DR. RUDOLF AEBLI: It was a pleasure to listen to this presentation, and we should be grateful that Dr. Bonaccolto presented this new and ingenious method of using metal rings to prevent vitreous loss in cataract surgery. Last October, at the Gailey Eye Clinic, on the 10th anniversary meeting of the Central Illinois Ophthalmological Society, Dr. Harold E. Henkes, of Rotterdam, Netherlands, showed some movies of this operation and reported good results.

The basic idea of the metal ring is to prevent any pressure on the globe by utilizing forward traction and suspending the eye. The ring must be firmly fixed to the sclera at 10, 2, 4, and 8 o'clock. I have not personally performed this operation and hence cannot speak from experience.

My impression is that use of the ring complicates the operation and only adds maneuvers that could go wrong. The firm anchorage of the ring to the sclera at 10, 2, 4, and 8 o'clock is not as easy as it sounds. Dr. John Wheeler said, "When simple procedures suffice, do not make the operation complex."

I feel that the careful and meticulous preparation that Dr. Bonaccolto employs, namely, complete akinesia, muscle cone injection, canthotomy in selected cases, lid sutures, and adequate sedation, contributes a great deal in avoiding pressure

on the globe and accounts for his good results, irrespective of whether or not he uses the ring.

DR. G. BONACCOLTO: I agree with Dr. Aebli that the support is an additional complicating factor, but it does not necessarily complicate the operation. Actually, I was not interested in the average cataract case. The average case does not require a ring, and most of us would not use one. But I was curious to try it in a number of selected and complicated cases—cases where we usually have trouble with subluxated lenses or protruding eyes, or where the patient, no matter how careful we are in the preparation, is nervous, as well as cases in which we cannot succeed in having a good aperture and a good exposure of the field. In such instances the ring really helped, and I do believe that Dr. Flieringa (*Am. J. Ophth.* 36:1618-1619, 1953) has brought us something of value in these cases of complicated intraocular operations.

The ring is also particularly useful in difficult cases of keratoplasty because the eye remains fixed and in position without increasing intraocular pressure. Castroviejo, in a personal communication, agreed with me on this point.

I believe we should welcome the ring to our armamentarium of surgery and try it in more of these special ocular cases.

Differential Electroretinography as a Measure of Macular Function. DR. JERRY H. JACOBSON, DR. DEMIR BASAR, and DR. ABRAHAM KORNZWEIG.

An attempt was made to differentiate the rod from the cone electroretingram by virtue of the differential responses of rods and cones to varying spectral light stimuli.

Since the cone function is more sensitive to the long end of the spectrum than the rod function, a group of normal subjects were tested, using a deep-red monochromatic light. Each of these normals showed a definite electroretinographic response. A group of 37 patients with macular disease were studied under the same conditions, and each showed no measurable response. It is inferred that this method may be a means of objectively determining macular function.

Discussion

DR. ABRAHAM KORNZWEIG: It is a pleasure to be associated with Dr. Jacobson in this very interesting and pioneering type of experimental research. I always feel that the physiocists and chemists are eventually going to take over medicine for us, and we shall be their hand boys or handmaidens. The contribution which I have to make to this particular study has been in getting the cases of macular degeneration, and I thought it would be of interest to show photographs of some of these fundi, of which we have been able to take pictures. We have been able to get these photographs before the patients were tested. I am going to show a few of the cases which were sent in from the Home for the Aged and Infirm Hebrews with these macular lesions. We have, as some of you know, been doing a considerable amount of work on the eye in old age, and we have been accumulating these fundus pictures, and are very happy to have in our group several cases which have been tested by Dr. Jacobson.

The photographs illustrate several varieties of macular degeneration, namely, senile macular degeneration, disciform macular degeneration of the Kuhnt-Junius type, diabetic retinopathy with macular degeneration, and the type associated with extensive arteriosclerotic and hypertensive retinopathy.

Concurrence of Macular Edema and Cataract Extraction. Dr. John V. V. NICHOLLS, Montreal, Canada (by invitation).

Though by its very nature macular edema might be expected commonly to follow cataract extraction, there is very little mention of it in the literature. Nine cases in eight patients are reported. In five of these the macular edema occurred some time after operation, whereas in four it probably occurred at about the same time. One patient showed a picture typical of senile macular degeneration, and another was highly myopic. In three cases the picture was suggestive of central angiospastic retinopathy.

In four patients there was a prolapse of vitreous through the pupil. In two of these the prolapse took place some time after operation and at about the same time as the macular edema. In another the prolapse and edema occurred at about the same time and almost immediately after operation. In the fourth vitreous was lost at operation and the edema occurred about six months later.

It is suggested that the predisposing cause of the macular edema was vascular instability in the retina and/or choroid in that region, partly brought about by cataract extraction. Also it should be noted that five of these patients had vascular hypertension to some degree. It is suggested that possibly the precipitating cause in some cases was anxiety, producing vasospasm, while in others prolapse of the vitreous through the pupil played a part.

The point of practical significance is that the end-result was good. All but one patient showed great improvement. Four patients recovered, even though given no treatment. Vasodilators do no harm, but there is no strong evidence in these cases that they do any good.

Discussion

DR. JOHN H. DUNNINGTON: This interesting presentation offers much food for thought. As the author states, the relationship between cataract extraction and subsequent macular edema is a complex one. Most of us have encountered cases of this type; yet few, if any, have become interested in trying to determine the exact cause. Dr. Nicholls made a painstaking analysis of his cases and interpretation of the causative factors. He has stressed the lowness of the nutritional reserve of the macular region and correctly used this fact as supportive evidence of the vascular origin of most of these lesions. In attempting to explain the reason for this circulatory disturbance, he expresses the belief that anxiety frequently is the precipitating factor. It seems to me that if fear were the cause this condition should occur frequently and make its appearance early in the convalescent period. The high incidence of arterial hypertension in all patients between the ages of 65 and 89 speaks against the etiological significance of this finding. Since the adoption of the intracapsular technique, we have become much more conscious of the importance of changes in the anterior face of the vitreous. The irritative phenomena that follow a sudden rupture of the hyaloid membrane are emerging as a clinical entity. There is often associated with such a forward displacement of the vitreous a transient reduction in vision, which is usually attributed to opacification of the vitreous. I wonder whether we can always exclude the presence of a macular edema. In some of Dr. Nicholls' cases the vitreous face remained flat, whereas in others he noted a forward displacement and rupture of the hyaloid membrane. This finding led him to believe the changes in the vitreous were not responsible for the macular edema—however herniation of the anterior face of the vitreous in the presence of an intact hyaloid membrane is often evanescent. Frankly, I do not know the significance of the changes in the position of the vitreous but believe it is worthy of further investigation. To the causes already mentioned can be added hypotony after cataract extraction. When this occurs as a complication of delayed or intermittent fistulization of the operative wound, macular edema is a frequent finding. The diagnosis of this condition is often overlooked and its presence not suspected because the anterior chamber usually is of normal depth and no choriodal detachment exists. The history of these cases is strikingly similar to that in some of the cases given by Dr. Nicholls. The operation and immediate convalescence are uneventful. A period of normal vision is followed by intermittent lacrimation, photophobia, mild iritis, vitreous opacities, and edema of the macula. The striking difference is that in these cases spontaneous cure does not occur and epithelization of the anterior chamber is a common end-result. These cases are not to be confused with the group Dr. Nicholls has presented, but are merely mentioned for completeness.

DR. JOHN V. V. NICHOLLS: Thank you, Dr. Dunnington, for your very careful and generous comment. I think that of late I am beginning to agree with what Dr. Dunnington has just said. It is possible that I have been overemphasizing anxiety, perhaps because of my early interest in central angiospastic retinopathy.

The more I have followed these patients, the less I think anxiety is involved. It may play a part, but it must be a very small one.

I would say, however, there is one thing which should be evaluated, and very carefully evaluated. It is the stability of the peripheral vascular system, not only of the eye, but of the whole body. I noticed in Irvine's paper (*Am. J. Ophth.* 36:599-619, 1953) in which there was a painstaking analysis of hundreds of cases, no mention was made of the results of physical examination in any he reported. I think it is very important that these patients should be considered not only as patients with cataract but as patients possibly having other diseases. It might be interesting to know what percentage of Irvine's patients had indications of peripheral vascular instability.

Regarding hypotony from fistulization, I did think of it, but I disregarded it in my discussion this evening because not one of my patients showed any evidence of it. I believe, however, that it is possible for there to be a subclinical form of fistulization of the corneoscleral wound, which is not evident to the examiner. Irvine's sections showed that the inner aspect of the corneoscleral wound may take weeks to heal. It is quite possible that here a pinpoint fistulization may take place, and go unnoticed.

The recent paper of Mitsui and Sakanashi (*Am. J. Ophth.* 41:105-114, 1956) is most interesting. They showed by slit-lamp examination that there is an actual detachment of the retina at the posterior pole in central angiospastic retinopathy! Though I have looked at many posterior segments, I have not been able to see the picture they described. Maybe my slit lamp is not good enough, or perhaps I am not a good enough observer, but I have not been able to observe such changes. Their findings might well account for some of the pictures described by me, and are very similar to what Dr. Dunnington has described in his case this evening.

Orbital Tumors of Childhood. Dr. Cecil W. Lepard, Detroit.

The clinical findings of orbital tumors occurring in childhood are of special interest because these children often come to the ophthalmologist for diagnosis.

There are important things to look for in the lids, the orbital structures, and the eye itself. There are often significant findings in the general physical examination, in the blood, and in the x-ray examination which may give one a clue to the diagnosis.

The signs of a mass or a space-taking lesion in the orbit are proptosis of the eye, limitation of ocular excursions, displacement of the globe, palpitation of a mass between the globe and the rim of the orbit, and changes in the disc and retina. Papilledema may occur when the tumor occupies a position within the anterior portion of the muscle cone.

Chloroma is an orbital manifestation of myelogenous leukemia. Palpable masses at the upper orbital margins are characteristic. Gross pathological findings are greenish-gray tumors, usually found at the roof of the orbits, but attached to the periosteum in other areas as well. Microscopically, these are masses of early forms of white blood cells.

Neuroblastoma of the orbit occurs as a metastasis from the cortex or medulla of the adrenal. Ecchymosis of the skin of the eyelids and subconjunctival hemorrhages are typical. Roentgenograms show destructive areas in the skull and orbit, with sunburst pattern in the skull. Examination of the abdomen reveals an enlargement of spleen and lymph nodes as an early sign. The degree of malignancy varies with the cell origin. The cell type is an undifferentiated, primitive migrating cell from the neural crest. These cells can be identified in the bone marrow early in the course of the disease.

Eosinophilic granuloma may be found in one orbit or in other areas of the skull on x-ray examination. The areas appear as round, punched-out, sharply demarcated areas. When curetted the material consists of necrotic cells with scattered eosinophiles. These granulomas tend to recur in other bone areas. X-ray therapy is sometimes effective.

Hand-Christian-Schüller-Disease is a related, but more advanced, stage of eosinophilic granuloma. The disease syndrome is characterized by generalized

xanthomatosis and diabetes insipidus. Roentgenograms studies show areas of destruction in the skull and long bones with punched-out, sharply demarcated borders. The pathological findings in the orbits are yellowish, firm masses of xanthomatosis material. These orbital tumors result in proptosis of one or both eyes.

Discussion

DR. JOSEPH A. C. WADSWORTH: The question of chloroma, which was typically described as a tumor in young girls, has fortunately become extremely rare. The general pathology department at the Presbyterian Hospital has not seen a case in a number of years. Even in the more recent literature, the recommendation is to establish a diagnosis and give no further treatment. It was interesting to see the marked improvement in the appearance of the child with chloroma whom Dr. Lepard showed; at least it is helpful for the morale of the patient, as well as the family, during the course of the disease.

With regard to the xanthomatosis diseases, the three are probably different manifestations of the same disease—Letterer-Siwe disease. Hand-Christian-Schüller disease, and eosinophilic granuloma. Letterer-Siwe disease is the most malignant of the three; it manifests itself by numerous nodules of endothelial growth. The Hand-Christian-Schüller disease is the next most malignant, and it is fatal, but of longer duration, and eosinophilic granuloma is actually a more or less benign tumor. In many instances it has shown spontaneous regression, or with complete or partial excision there has been no recurrence of the disease. The theory has been advanced in these reticuloendothelial tumors that the process is a matter of inflammatory response, possible due to a virus, but that is not usually accepted by the men doing the most work on this subject.

The question of neuroblastoma—one has the classification of the Hutchinson and the Pepper type. The people doing the most work on this tumor feel that this is an arbitrary division, because most of the cases at the end will show manifestations of both the Pepper and the Hutchinson type. It is remarkable that Willis, in his very complete report on neuroblastoma, did not note the orbit as one of the sites of metastasis, but mentioned practically every other organ in the body and the bones of the skull. It is quite frequently found that the orbit may be the first manifestation of the disease, as Dr. Lepard mentioned.

It is also interesting that with the malignant tumor of the kidney, Wilms' tumor, neuroblastoma is considered to be the commonest malignant tumor in children.

DR. CECIL W. LEPARD: There is a great variety in neuroblastomas, in the degree of their malignancy, and I agree that the more recent thinking is that the Pepper type and the Hutchinson type are one and the same, and that they should not be differentiated into the two groups.

Maynard C. Wheeler, M.D., Chairman
Harold W. Brown, M.D., Secretary
March 19, 1956

Retinal Microaneurysms. GEORGE N. WISE, M.D.

Mackenzie and Nettleship in 1877 first reported the capillary microaneurysm in the retina of a diabetic patient. This observation was then "lost" until 1943, when Ballentyne and Lowenstein rediscovered the lesion also in diabetic retinoparthy. Ashton's vascular injection technique and Friedenwald's application of the Hotchkiss-McManus stain have greatly added to our knowledge of these microaneurysms.

They have now been reported not only in diabetic retinopathy but also in such diverse retinal conditions as venous thrombosis, thrombotic glaucoma, chronic glaucoma, Eales' disease, hypertension, arteriosclerosis, chorioretinitis, pernicious anemia, carcinoma with anemia, sickle-cell anemia, retinoblastoma, and, occasionally, in normal retina.

There was considerable controversy at first as to whether the microaneurysms occurred on the arterial or the venous side of the capillary network. Omitting the details of this debate, I may say that more recently the consensus of opinion has placed them predominantly on the venous side of the circulation.

Morphologically, they have been described as bulges, sacules, elongated pouches, and bizarre forms varying from 30μ to 90μ in diameter. All had a definite basement membrane, and an endothelial lining was usual. Often several were seen on one side of a capillary, the wall opposite being completely normal. They arose predominantly from the capillaries connecting the deep and superficial capillary beds. They were often surrounded by a zone of hemorrhage and were associated at times with dilated capillary channels, sausage-shaped capillaries, and loops and coils in the regional capillary network. With the passage of time they often underwent lamellar hyalinization, obliteration, and ultimate absorption.

Some authors have considered those microaneurysms occurring in diabetic retinopathy specific. However, these same investigators have reported microaneurysms in other conditions indistinguishable from those in the diabetic retina. Today majority opinion holds that there is no essential difference between the variable forms of microaneurysms found in the diverse conditions enumerated above.

Ashton explained their development by a looping of the capillary channel with subsequent disappearance of the central reduplicated wall and a final straightening out of the wall opposite the loop. The loop thus became a microaneurysm.

Becker and Post regularly produced retinal microaneurysms in the cat following diathermic obstruction of the central retinal vein. The aneurysms occurred in large numbers and were identical with those seen in human pathology. Other than this they have not been regularly reproduced experimentally.

As to pathogenesis, Friedenwald felt they were not due to hypertension or arteriosclerosis per se and that they did not result from an increased capillary pressure. Ashton stated that they were true aneurysms. Those occurring in uveitis with glaucoma he considered due to a toxic action of the uveitis on the capillary wall, those in venous thrombosis due to capillary wall degeneration, and those in his case of retinoblastoma he felt were associated with the abnormal vascular growth of this tumor. Majority opinion at present favors initial capillary wall damage and secondary microaneurysm formation.

Several findings argue strongly against this view. First, microaneurysms were often found in the absence of any visible wall damage. Second, they were sometimes not present where capillary wall damage was seen. Third, they often arose from one side of a capillary, the opposite wall of which was entirely normal. Finally, no single cause has thus far explained their regular occurrence in the diverse conditions in which they have been found.

Before proceeding further with this discussion, it is well to briefly review Michaelson's superb work on the development of the retinal circulation in man.

The early retina is supplied entirely from the choroidal circulation. As the retina develops and thickens vascular buds grow out from the primitive central retinal vessels at the disc. These developing vessels progress in an orderly manner to form the superficial vascular bed lying in the nerve fiber layer. As the retina further thickens, downshoots from this first retinal vascular layer progress to form a second, deeper vascular layer. This process continues until at term the definitive retinal vascularization is complete. All vessels grow from preexisting vessels; no local cell differentiation occurs. Two things are of great importance, (1) all capillaries develop entirely from veins and (2) four areas remain avascular in the fully developed retina. These four areas are the outer retina layers, a periarterial zone, a zone at the ora, and one at the fovea. All are of the same approximate width and all are adjacent to a satisfactory arterial blood supply.

These findings led Michaelson to conclude that the capillaries and veins should be included in one vascular unit. The arteries would therefore comprise a second such unit. Also from this data he elaborated a theory that vascular growth, primarily from the veins and capillaries, occurred in response to the development of some unknown factor, x, arising in areas of relative retinal anoxia. The growing blood vessels satisfied the anoxia, caused the disappearance of

Factor x, and restored equilibrium, and, as a result, vascular growth eventually ceased. Michaelson felt that this fetal capacity of capillaries and veins to form new blood vessels did not disappear at birth but simply lay dormant.

What single clinical condition might cause the relative anoxia necessary to produce Factor x and reawaken this dormant capacity of veins and capillaries to form new blood vessels in the mature retina?

In a three-year study of retinal neovascularization which we have undertaken at New York University, venous obstruction seemed to meet the requirements of this question. Arterial obstruction led to anemic infarction, excessive retinal anoxia, and tissue death. On the other hand, venous obstruction, regardless of its mechanism of development, led to circulatory stagnation and stasis. The resulting relative retinal anoxia, insufficient for massive tissue death but great enough to stimulate the development of Factor x, reawakened this dormant capacity of veins and capillaries to form new blood vessels.

Neovascularization from obstructed veins and capillaries in venous thrombosis has been demonstrated in pathologic section. Ballantyne has shown conclusively that the rete mirabile type of retinal neovascularization developed from obstructed veins and capillaries in diabetes. Ashton and others have shown this same phenomenon in experimental retrolental fibroplasia, and the same mechanism has been demonstrated in pathologic section in cases of Eales' disease.

Neovascularization from the retina in cases of malaria, polycythemia, sarcoid, and sickle-cell anemia is incident to the capillary and venous obstruction of these diseases. The latter disease deserves special mention.

In patients having sickle-cell anemia or the sickle-cell trait, the sickling phenomenon is increasingly pronounced in zones of low oxygen tension. With sickling the red blood cells become rigid and unable to pass through capillaries and small vascular channels. Vascular obstructions thereby result, and these are commoner in capillaries and small veins because of the lower oxygen tensions at such points. It is most interesting that both neovascularization and microaneurysms have been reported in this disease. Some of these were cases in young adults apparently free of other vascular or retinal disease. The site of the vascular obstruction in sickle-cell anemia is identical with that thought to occur in early diabetic retinopathy.

The most striking finding in our study of retinal neovascularization was the constant association of microaneurysms with new blood vessel formation. These minute retinal lesions were usually missed in fundus examination by the ordinary battery ophthalmoscope. They were readily seen however, with the intense illumination of the giant A.O. ophthalmoscope. Indeed many lesions appearing to be small blot hemorrhages were noted by this means to actually be fine networks of retinal or preretinal neovascularization. Retinal microaneurysms and new blood vessels were found to be two of the commonest residua in the fundus after uncomplicated venous thrombosis.

This finding suggested a new theory as to the nature and pathogenesis of these lesions. The theory explained their frequency in some conditions, their infrequency in others, and their occasional sector-like distribution and proposed one common mechanism for all.

These lesions are not actual aneurysms but represent aborted attempts at neovascularization. Either a minimal retinal anoxic tissue stimulus is satisfied by their bulge toward the stimulating point and the coincident better oxygenation of this area or new blood vessels growing from adjacent more strongly stimulated veins and capillaries reach the anoxic area first, satisfy the relative retinal anoxia present, and restore equilibrium and neovascular growth ceases, leaving these aborted neovascular buds in its wake.

What evidence supports this theory?

1. The embryonal capillary bed, the new blood vessels in retinitis proliferans of the mature retina, and retinal microaneurysms all develop from the same general site—the venous side of the circulation, particularly from capillaries and venules.

2. Both the frequent development of aneurysms from one side of a capillary wall and the beading of capillaries can be explained by this theory. In the former, the stimulated capillary lies to one side of the stimulating anoxic area and the neovascularizing effect exerts its force on the more proximal capillary wall. In the latter, the capillary lies within the anoxic area and the vascular stimulating effect is exerted on both walls of the capillary, resulting in beading. Note the similarity of this to Michaelson's finding in the developing retinal capillary bed. If a fetal vein and artery lie near one another, the capillary vessels arise from the side of the vein opposite the artery and grow toward the area of relative retinal anoxia. The artery, with its better regional oxygenation, tends to inhibit blood vessel growth in its direction.

3. Embryonal retinal vessels have a basement membrane which stains poorly with Hotchkiss-McManus stain. However, aneurysms and new blood vessels in both human and experimental retrolental fibroplasia take this basement membrane stain vividly.

4. Aneurysms are often seen in regions where there is no capillary wall damage. They are likewise not present in some areas of obvious capillary wall pathology. This indirect evidence points to some factor other than capillary wall pathology as being of prime importance in their pathogenesis.

5. Aneurysms can be seen clinically and have been shown in pathologic section to occur in areas where neovascularization is present. This suggests a common pathogenesis for both. If aneurysms are not early neovascular formations, then where are the latter in such areas?

6. While microaneurysms do not result from venous obstruction per se, it is the mechanism par excellence for setting the retinal stage for their subsequent appearance. Thus they are found in greatest numbers in venous thrombosis, thrombotic glaucoma, diabetes, Eales' disease, chronic glaucoma, and severe hypertension, especially malignant hypertension. In venous thrombosis and thrombotic glaucoma venous obstruction is obvious. Ballantyne and others have shown both venous and capillary obstruction to be a prominent early feature of diabetic retinopathy and a constant finding in diabetic retinitis proliferans. It has also been shown to be regular feature of Eales' disease, secondary to the periphlebitic inflammatory process of this disease. Both Verhoeff and Salzmann have shown a very high incidence of vascular obstruction in chronic glaucoma, particularly obstruction of veins. The increasing incidence of both branch and central vein obstruction, the severer the degree of hypertension, is a well-known clinical fact. Thus all of these various conditions have in common a high degree of venous obstruction. Also, all usually show large numbers of retinal aneurysms.

7. The sporadic occurrence of microaneurysms in other conditions is also explainable by this theory. The milder degrees of venous obstruction and stasis in the less severe cases of hypertension and in cases of arteriosclerosis would be expected to elicit fewer microaneurysms in such retinae. Such are the usual findings. The retina is known to have an extremely high rate of oxygen consumption, equal to that of some tumor tissues. Is it not conceivable that severe anemias might so lower the retinal oxygen supply as to bring on a state of relative retinal anoxia in scattered areas? Such areas would then be prompted to develop sufficient Factor x to call forth the sporadic microaneurysms reported in these conditions.

8. The sector distribution of retinal microaneurysms is explained on the basis of branch venous obstruction with subsequent development of aneurysms in the obstructed area. We have repeatedly seen this clinically in the careful search with intense illumination. At least one of Ashton's cases demonstrates it nicely. Indeed, the sector distribution of multiple microaneurysms in cases of chorioretinitis is undoubtedly due to the venous obstruction secondary to such zones of intense inflammation. Knapp called attention to this phenomenon of venous obstruction secondary to chorioretinitis. It is not an unusual clinical entity. Reese and Guyton showed beautiful drawings illustrating clinically visualized microaneurysms in obstructed venous sectors of patients with Eales' disease. Ashton, in reporting multiple microaneurysms in a globe containing a melanoma, made special mention of the fact that the tumor secondarily obstructed the retinal

veins. The most likely explanation of the finding by Ashton of microaneurysms within a retinoblastoma is the undoubted high oxygen consumption of such tissue, the development of relative anoxia and Factor x therein, and the subsequent neovascularization and aneurysm formation. Thus this theory can explain the sector-like distribution of microaneurysms demonstrated in certain cases.

9. According to this theory, why then should no microaneurysm be found in retrolental fibroplasia?

In this disease there is vaso-obliteration of both arteries and veins of the retina. On return to air many vascular channels fail to reopen because of adherence of their internal walls. Probably more veins remain closed than arteries because of their thinner, less resilient walls and lower internal pressure. Thus, a situation of massive venous and some arterial obstruction obtains. Under such circumstances the marked relative retinal anoxia causes a marked development of Factor x with its overwhelming neovascularization stimulus. All neovascular buds progress to fully formed new vessels; none cease development in their early stages, and no microaneurysms are left.

Ashton was able to prevent coaptation of the vascular walls in the vaso-obliteration phase of experimental retrolental fibroplasia by the use of anticoagulants. No neovascularization occurred in the few cases so treated. This finding supports the importance of vascular obstruction in neovascularization and aneurysm formation.

As would be expected, "aneurysms" or aneurysmal dilations are found in retrolental fibroplasia at the terminals of the newly developing blood vessels. This is well shown in some of Reese's illustrations of the early pathology of human retrolental fibroplasia. The aneurysmal-like bulbs at the tips of intravitreous neovascularization in diabetic retinitis proliferans have been noted by Friedenwald. We have noted these bulbous dilatations clinically at the tips of intravitreous new blood vessels in venous thrombosis, diabetes, and Eales' disease. It is interesting that Ashton's description of the mechanism of formation of microaneurysms may well represent a common method of new blood vessel growth. It is certainly a frequent observation in retinitis proliferans to see a brush of rather straight vessels projecting into the vitreous, only to become very tortuous, twisted, and folded toward their termination in a final bulbous loop.

Aneurysmal-like ectasias can be produced in experimental retrolental fibroplasia by stopping the neovascularization at an early stage. This is well illustrated by Ashton, Ward, and Serpill, who injected a post-vaso-obliteration kitten retina after only a short interval in air. The retina was literally laden with these aneurysmal-like neovascular buds.

10. Finally, retinal microaneurysms quite similar to the human ones have been produced experimentally by Becker and Post regularly and in great numbers by diathermic obstruction of the central retinal vein of the cat. They have not been so copiously produced experimentally in any other way thus far.

In summary, retinal neovascularization proceeds primarily from veins and capillaries in response to the development of Factor x in areas of relative retinal anoxia. The reawakening of the dormant fetal capacity of veins and capillaries to form new blood vessels is primarily brought about in the mature retina by venous obstruction. So-called retinal microaneurysms are actually aborted attempts at new blood vessel formation.

Discussion

DR. ANTHONY DONN: If you postulate that anoxia alone is the stimulus for capillary budding and hence for so-called microaneurysms, how do you account for the characteristic presence of microaneurysm in diabetes? I do not believe that diabetic tissue, in the absence of a vascular accident, is supposed to be anoxic. Would it not be more likely that the stimulus for capillary budding in diabetes is carbohydrate starvation of the tissues?

DR. WISE: Ballantyne and others have clearly demonstrated that capillary and venular obstruction or stasis are among the earliest pathologic changes in diabetic retinopathy. This would indeed lead to carbohydrate starvation as well as anoxia. No one can yet say what Factor x is. However, in the presence of

capillary or venous obstruction, in conditions where there is no derangement of carbohydrate metabolism, capillary budding just as regularly occurs.

DR. CHARLES A. PERERA: Can you differentiate between new-formed capillaries and dilated preexisting ones?

Are you acquainted with work suggesting that new-forming vessels may start out as solid plugs of endothelial cells which became canalized later?

DR. WISE: Intraretinally it is very difficult to distinguish between the two. Intravitreous blood vessels present no problem. Since the stimulus for the development of both is probably the same, I have considered the question primarily academic and have thought of the two as one entity.

In answer to the second part, I can only agree with Dr. Perera that there is probably more than one mechanism of new blood vessel formation.

News and Comment

ANNOUNCEMENTS

University of Florida Midwinter Seminar.—The Eleventh Annual University of Florida Midwinter Seminar in Ophthalmology and Otolaryngology will be held Jan. 14-19, 1957. As in previous years, Miami Beach will be the host city.

The lectures on Ophthalmology will be presented on Jan. 14, 15, and 16. The lecturers for the courses in ophthalmology will be such distinguished ophthalmologists as Drs. Irving H. Leopold, Philadelphia; Cecil W. Lepard, Detroit; Francis Heed Adler, Philadelphia; Algernon B. Reese, New York, and Harold W. Brown, New York.

Outstanding teachers who will lecture on Jan. 17, 18, and 19 are Drs. Alden H. Miller, Los Angeles; Porter P. Vinson, Richmond, Va.; Lester Hale, Gainesville, Fla.; James B. Costen, St. Louis, and Philip Meltzer, Boston.

Urgent Request.—The Uveitis Laboratory, University of California School of Medicine, San Francisco, is anxious to obtain freshly enucleated eyes from patients with all types of uveitis and endogenous uveitis. We are making attempts to isolate viruses and other etiologic agents from these eyes. We are also interested in pathologic studies to aid in identification of any agents. In addition to eyes with the usual types of uveitis, we are interested in those which develop intraocular inflammations as a result of sclerosing keratitis, herpes febrilis and zoster of the cornea, mycotic corneal infections, glaucoma secondary to endogenous uveitis, Coats' disease, Eales' disease, papillitis, and scleritis. The eye tissues will be cultured in various media.

The eyes should not be fixed in preservatives or frozen, but placed in a sterile bottle, packaged, and shipped as quickly as possible. Please send the specimens air express, special delivery, collect. Enclose history and findings and mark the package "Fresh Tissue Specimen—Rush."

A report of isolations of organisms and pathologic findings, including a slide, will be sent to the contributor, and credit will be given in any resulting publications if desired.

Please telegraph collect if a specimen is being sent. Send eyes to Samuel J. Kimura, M.D.; Michael J. Hogan, M.D., or Phillips Thygeson, M.D., University of California School of Medicine, San Francisco 22.

Gill Memorial Eye, Ear and Throat Hospital Congress.—The Gill Memorial Eye, Ear and Throat Hospital, in Roanoke, Va., will hold its 30th Annual Spring Congress in Ophthalmology and Otolaryngology and allied specialties, April 1 through April 6, 1957.

Among the guest speakers who will attend are the following:

Dr. David B. Allman	Atlantic City
Dr. Seymour Albert	Washington, D. C.
Dr. Edward A. Carr Jr.	Ann Arbor, Mich.
Dr. James H. Doggart	London, England
Dr. Harold F. Falls	Ann Arbor
Dr. Frederick A. Figi	Rochester, Minn.
Dr. Samuel Fomon	New York
Dr. Dan M. Gordon	New York
Dr. Maynard K. Hine	Indianapolis
Dr. Howard P. House	Los Angeles
Dr. Jay G. Linn Jr.	Pittsburgh
Dr. Frank W. Newell	Chicago
Dr. Hugh L. Ormsby	Toronto, Canada
Dr. Albert D. Ruedemann	Detroit
Dr. Harry L. Rogers	Philadelphia
Dr. Frank B. Walsh	Baltimore
Dr. Barnes Woodhall	Durham, N. C.

New Orleans Academy of Ophthalmology.—The Midwinter Convention of the New Orleans Academy of Ophthalmology will take place Feb. 11-15, 1957. The program will feature a Symposium on Glaucoma by Drs. Bernard Becker, W. Morton Grant, Joseph S. Haas, A. E. Maumenee, Harold G. Scheie, Kenneth C. Swan, and Georgiana D. Theobald.

The registration fee of $75.00 includes associate membership in the New Orleans Academy of Ophthalmology for the year 1957, as well as all other features of the convention.

SOCIETY NEWS

Trachoma Meetings: 1956.—The meetings of three organizations dedicated to the struggle against trachoma took place in April and May of this year.

I. Meeting of the International Organization Against Trachoma, Madrid, April 26, 1956.

This organization held a meeting at University City in Madrid on April 26 in connection with the Second Congress of the Latin Society of Ophthalmology and under the honorary chairmanship of Prof. Buenaventura Carreras-Duran, director of the eye clinic of the University of Madrid and president of the Second Congress, and of M. Boone, director of the Division of Services for Communicable Diseases of the World Health Organization.

After the address of Prof. G. B. Bietti, director of the eye clinic of the University of Rome, as president, and the report of the secretary-general, Jean Sédan, the following papers were presented and discussed:

1. Professor Marin-Amat (Madrid): El tratamiento quirurgico del tracoma: su importancia en la lucha antitracomatosa actual
2. Poleff (Rabat): Insuffisance des méthodes actuellement employées dans la lutte contre le trachome des masses et perspectives d'avenir
3. Ferraris de Gaspare (Rome and Hofuf A. S.): Considérations sur les résultats des interventions antiglaucomateuses chez les trachomateux
4. Jean Sédan (Marseille): De l'efficience du tannage pour l'entretien de la cicatrisation trachomateuse, reconsiderée après une pratique de vingt-cinq ans
5. A. Milano (Naples): Chimiothérapie du trachome
6. Emilio Gil del Rio (Vitória): Frequencia y causas del tracoma en el pais Vasco
7. B. Boles-Carenini and A. Cambiaggi (Cagliari): Les veines aqueuses dans le trachome

These papers were discussed by Drs. Pages (Rabat), Sohby (Cairo), Jean Sédan (Marseille), G. B. Bietti (Rome), Maxwell-Lyons (World Health Organization, Geneva), Mabrouk (Tunis), and Marin-Amat (Madrid).

The International Organization Against Trachoma will hold its next meeting in Brussels in 1958 at the time of the International Congress of Ophthalmology.

II. Meeting of the Trachoma Discussion Group of Paris, May 5, 1956.

The meeting of the Trachoma Discussion Group was called together on May 5 at the home of President Bailliart by the secretary-general of the League Against Trachoma, Jean Sédan. The subject for discussion was "The Duration of Treatment in Trachoma."

The participants in the discussion were Prof. G. B. Bietti (Rome), Pages (Rabat), Roger Nataf (Tunis), Rheinards (World Health Organization, Geneva), Svetozar Postic (Novi Sad, Yugoslavia), Jeandelize (Nancy), Olga Litricin

(Belgrade), Stankovic (Belgrade), Jean Sédan (Marseille), Eddie Mawas (Paris), Chalvignac (Marrakech), and Maggiore (Geneva).

It was concluded that after a three-week to three-month period of regular, controlled treatment cures must be estimated, but that all cases should be observed over a period of years.

The theme chosen for next year's Discussion Group Meeting was: "What should be the role of the old-time, classical methods of treating trachoma? Should they or should they not be combined with present-day methods?"

III. The General Assembly of the League Against Trachoma, Paris, May 7, 1956.

The General Assembly, with an important attendance representing 14 nations, met in the Centre Marcellin-Berthelot, which had most graciously been placed at its disposal, as it is every year, by the French Ophthalmological Society. The title of honorary president was conferred successively on Prof. Luigi Maggiore, of Geneva, and on Dr. Emmanuel Cornet, of Paris.

After the address of President P. Bailliart and the report of Secretary-General Jean Sédan, the Assembly voted to award the Medaille d'Or Chibret, with its purse of 200,000 francs, to Prof. Mario Giaquinto, of the Communicable Disease Service of the World Health Organization, with an expression of gratitude to the Organization itself. It then voted to award the Bourse d'Études Chauvin-Blache (200,000 francs) to Dr. Sohrab Darougar, an attaché of the Research Department of the Faculty of Tehran.

A discussion of the report of Roger Besnainou, of Tunis, on "The Surgery of Trichiasis" was then undertaken. Participating successively in this discussion were Prof. Jean Charamis (Athens), Professor Toulant (Algiers), Professor Larmande (Algiers), Prof. G. B. Bietti (Rome), Professor Stankovic (Belgrade), M. Pages (Rabat), Hadi-Rais (Tunis), Svetozar Postic (Novi Sad), Eddie Mawas (Paris), Jacques Mawas (Paris), Archimede Busacca (São Paulo), Roger Nataf (Tunis), and Rheinards (World Health Organization, Geneva).

The following free papers were then presented and discussed:

1. Emmanuel Cornet (Paris): Une classification unique et universelle du trachome
2. Jean Peyreblanques (Dax): Tumeurs cornéennes épithéliales et trachome
3. Roger Nataf (Tunis): Quatrième note sur "cortisone et trachome"
4. Rohrschneider (Munich): Zur Epidemiologie des Trachoma in Deutschland
5. Jean Sédan (Marseille): Résultats bactériologiques de la cure tannique des infections conjonctivales chroniques, survivant à la cicatrisation trachomateuse (second note)
6. François Malnou (Tozeur): Rôle du trachome dans la cécité du Sud-Tunisien
7. Stany Habachi (Cairo): Importance de la trachomatologie en ophtalmologie
8. Mabrouk et Maiza (Tunis): Premiers essais de traitement du trachome par l'achromycine
9. Svetozar Postic (Novi Sad): Le follicule trachomateux, sa signification pathologique et ses rapports avec le virus trachomateux
10. Olga Litricin and Milivoje Radovanovic (Belgrade): Du diagnostic différentiel de la folliculose et du trachome initial en Yougoslavie

11. Jean Charamis and Georges Tacticos (Athens): Données récentes sur l'évolution du trachome en Grece
12. Pages and Gouray (Rabat): Valeur du procédé de Trabut d'après 3,500 opérations

The General Assembly then agreed that the next reports to be presented to the League would be as follows:

1957: Prof. Jean Charamis (Athens): Le trachome lacrymal

1958: P. Thygeson (U. S. A.) and Roger Nataf (Tunis): The problem of the Etiology of Trachoma

1959: Prof. Marin-Amat (Madrid): Incidences du trachome sur les indications thérapeutiques dans les affections oculaires

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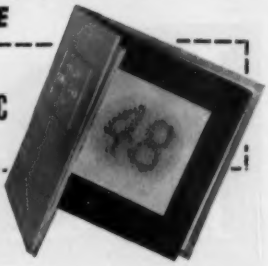

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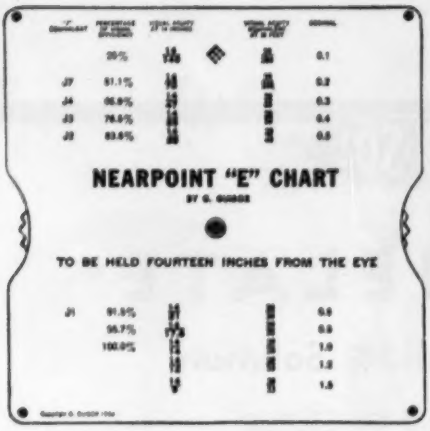

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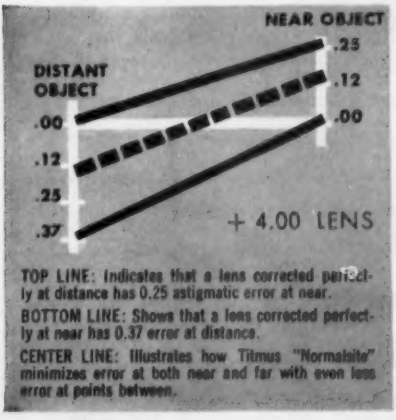

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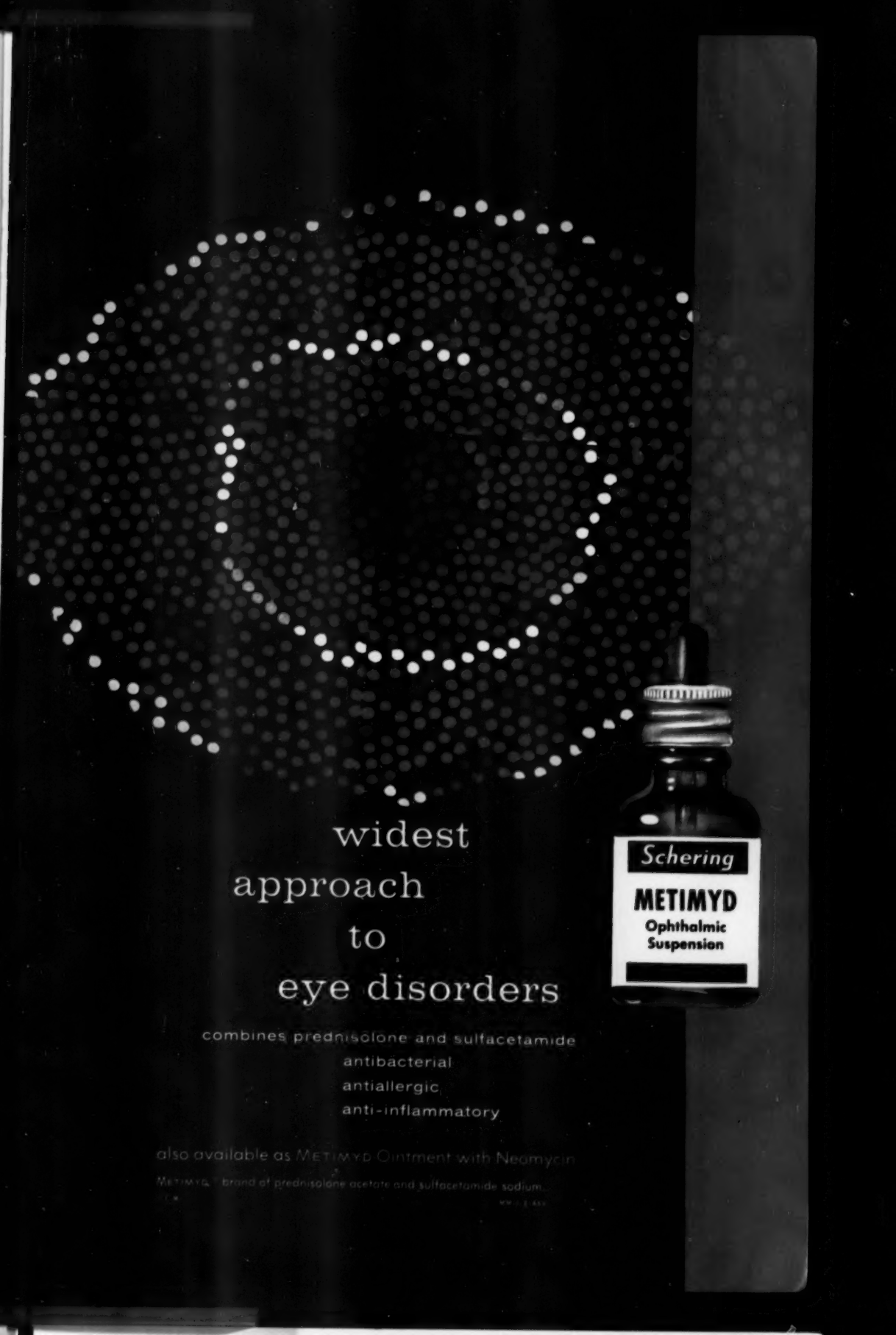
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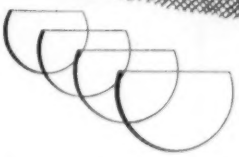

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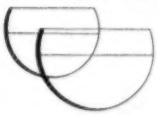

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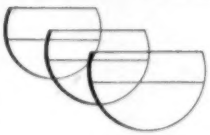

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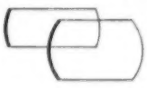

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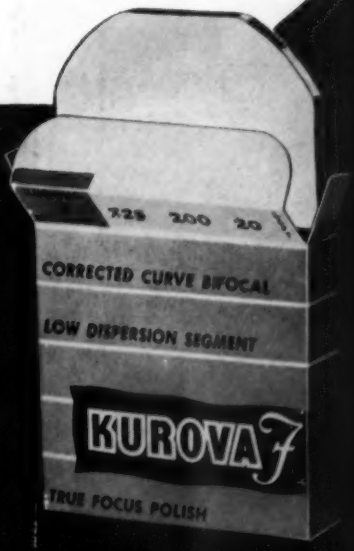

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